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Prize Lectures

The Geoffrey Harris Award Lecture

AP1

Translational Neuroendocrinology at the Crossroads of Reproduction and Metabolism

Manuel Tena-Sempere[1,2]
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Neuroendocrinology has astonishingly progressed since its inception, grounded on seminal findings of Prof. Geoffrey Harris in mid-20th century. A fascinating aspect of Neuroendocrinology for a young medical student as myself was the sophistication of the interactive neurohormonal mechanisms connecting key body functions, as metabolism, growth and reproduction. After 30-years in the field, I remain thrilled by these sophisticated systems. My research group is interested in dissecting the key pathways whereby our brain controls reproduction and energy balance, and how it decodes nutritional/ metabolic information to precisely integrate these fundamental bodily functions. Our focus is primarily basic research. In this domain, my team has actively analyzed the roles of kisspeptins and related neuropeptide systems in the control of puberty and fertility, and their interplay with metabolic signals and energy sensors, explaining the impact of conditions, such as obesity or subnutrition, on reproductive health. Despite our strong drive for basic research, my team has recently embraced more translational projects, aiming to exploit the potential applicability of our basic findings. This is illustrated by multiple research lines at my group, including the identification of novel molecular markers of metabolic health in pubertal children, and the search of new mechanisms and targets of intervention in common reproductive-metabolic disorders, as polycystic ovary syndrome and obesity-induced hypogonadism. These lines will be briefly overviewed in my presentation, also as a means to vindicate the value of translational neuroendocrinology, at the intersection between reproduction and metabolism, to tackle prevalent conditions, from obesity to pubertal disorders and infertility.

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The *European Journal of Endocrinology Award* Lecture

AP2

Abstract unavailable

DOI: 10.1530/endoabs.90.AP2

Clinical Endocrinology Journal Foundation Award Lecture

AP3

Chronotherapy in Congenital Adrenal Hyperplasia

Richard Ross
University of Sheffield, Sheffield, United Kingdom

A central tenet in medicine is that disruption of homeostatic mechanisms leads to disease and effective therapy must re-establish normal physiology. The sun imposes a 24-hour periodicity to life and circadian rhythms have evolved to maintain homeostasis through the 24-hour day/night cycle. In humans, there is a central clock that controls the sleep/wake cycle which metabolically is a fast/feed cycle. The clock maintains homeostasis by synchronising metabolism to the time of feeding; for example, regulating the hormones that maintain glucose homeostasis such as insulin and the glucocorticoid, cortisol. Loss of synchrony between the clock and hormonal rhythms results in loss of homeostasis as evidenced by obesity, depression, and diabetes in people undertaking shift work. Loss of the cortisol rhythm in congenital adrenal hyperplasia (CAH) results in poor disease control and increased mortality. To develop chronotherapy, you need to define the drug target rhythm, create a formulation to replicate that rhythm and then prove benefit in clinical trials. The physiology of hormones is more complex than that of non-native drugs. Hormones are secreted with varied rhythms, bound to multiple cognate binding proteins, and actively transported and cleared through enzymatic pathways in multiple organs. We have examined the diurnal rhythm of cortisol in healthy volunteers, created physiologically-based pharmacokinetic models, and tested various oral delayed and sustained formulations (development name Chronocort) of hydrocortisone in phase 1, 2 & 3 clinical trials. The output from this work is modified-release hydrocortisone (MRHC) capsules (tradename Efmody, Diurnal Ltd, Cardiff, UK) that replicate the cortisol diurnal rhythm and improve the disease control of CAH, the commonest hereditary form of adrenal insufficiency.ReferenceWhitaker MJ, Huatan H, Ross RJ. Chronotherapy based on modified-release hydrocortisone to restore the physiological cortisol diurnal rhythm. Drug Deliv Transl Res 2023;13:1-8.

DOI: 10.1530/endoabs.90.AP3

European Hormone Medal Award Lecture

AP4

The Parathyroid Hormone Saga: A Never Ending Story

Maria Luisa Brandi
FIRMO Foundation, Florence, Italy

Just before the turning of the 20th century a detailed series of connected events led to the understanding of the physiology, pathophysiology, chemical synthesis, cellular and molecular biology, and pharmacological use of parathyroid hormone (PTH) in the next 120 years. Thanks to scientists like Fuller Albright, Gerald D. Aurbach, John T. Potts, Karen K. Winer, Thomas J. Gardella, and many others, huge progress has been made over the decades through biotechnological advances to increase the medical knowledge regarding PTH. From 2002 the revolutionary pharmacological application of periodic administration of the PTH analog, teriparatide, in the treatment of osteoporosis opened to the development of PTH peptides as drugs to be used in bone and mineral disorders. After this success story a synthetic peptide of human PTH-related protein, abaloparatide, was approved for the treatment of osteoporosis. In 1994, before the development of teriparatide for osteoporosis, the first systematic investigation into synthetic human PTH 1-34 (later indicated as teriparatide) replacement therapy in hypoparathyroidism was launched. Only in 2015 human intact PTH was approved as the first hormone replacement therapy for treating hypoparathyroidism. The challenges ahead for medicinal chemists are to design compounds that affect the PTH receptor in a tissue selective manner. Such developments seem predictable, based on new advances in parathyroid research. ***"The saga of PTH will continue in the biotechnology of its analogs and the interest of pharmaceutical firms in this field's potential."***

DOI: 10.1530/endoabs.90.AP4

AP5

Abstract unavailable

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Jens Sandahl Christiansen Awards

JSC1

Altered splicing process in metabolic (dysregulation)-associated fatty liver disease (MAFLD) progression

Manuel Gahete
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Metabolic (dysregulation)-associated fatty liver disease (MAFLD) is the main cause of liver dysfunction, showing a prevalence of 20-30% in the general population and 57-74% among patients with obesity. MAFLD comprises a spectrum of chronic liver diseases, ranging from simple hepatic steatosis to non-alcoholic steatohepatitis or NASH, which can lead to advanced fibrosis and cirrhosis, increasing the risk of hepatocellular carcinoma (HCC). HCC is the most frequent, heterogeneous, aggressive and worst-prognosis primary liver subtype, representing 80-90% of all cases and exhibiting a 5-year survival rate of 17%. The development of HCC is a complex process that normally occurs in the context of chronic liver disease and cirrhosis, which has been recently shown to be closely associated with the presence of obesity and MAFLD. This represents a serious threat for global health in that the prevalence of obesity and MAFLD has increased dramatically and can lead to an increment of cases of advanced liver disease, cirrhosis and HCC. Therefore, we are trying to understand the cellular and molecular events associated to the development and progression of chronic liver disease. One of the most drastically altered biological processes during the progression of MAFLD is the processing of RNA and its alternative splicing. For

this reason, we are characterizing the landscape of spliceosomal (spliceosome components and splicing factors) changes occurring during the development and progression of chronic liver disease from MAFLD and NASH to HCC, as well as their molecular and clinical implications to identify novel molecular markers for the diagnostic and/or prognostic of the different stages of MAFLD, as well as therapeutic targets in the management of this prevalent pathology.

DOI: 10.1530/endoabs.90.JSC1

JSC2

Abstract unavailable

DOI: 10.1530/endoabs.90.JSC2

Plenary Lectures

PL1

Care of childhood cancer survivors

Stephen Shalet
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By 2010 one in 250 of the adult population was a long-term survivor of childhood cancer (CC). In 2014 there were an estimated 420,000 CC survivors in the USA alone(Robison et al.2014). In a follow-up study of 14,000 aging survivors of CC (Mostoufi-Moab et al 2016), in whom the median age at cancer diagnosis was 6 years and at the last Follow-up 32 years, 44% had a least one endocrinopathy,16.7% had at least 2 endocrinopathies and 6.6% had 3 or more endocrinopathies. The key documented modalities of treatment that induced these endocrinopathies are radiotherapy and certain forms of chemotherapy. Over the last 40+ years the following endocrine sequelae have been noted: Hypopituitarism, Thyroid dysfunction, Thyroid tumours, Hyperparathyroidism, Hypogonadism and Infertility, Osteoporosis, Insulin Resistance and Diabetes Mellitus. Newer treatments for certain malignancies such as Proton Beam Therapy for medulloblastoma (Yock et al. 2016), whilst achieving comparable survival figures to those seen after conventional radiotherapy, are still associated with significant endocrine deficits (63% at 7 years). In general, the Paediatric Endocrinologist is reasonably aware of the endocrine requirements, the efficacy of therapy, and the safety issues for CC survivors during childhood. However this is a relatively new field for the Adult Endocrinologist expected to look after these patients during adult life.

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PL2

Diagnosis and management of paraganglioma

William F. Young
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The first patient with a catecholamine-secreting paraganglioma that was sucessfully resected was in 1926. Over the past 97 years, there has been a dramatic evolution in the clinical presentation, methods used to diagnose and localize, and germline genetic testing of paragangliomas (PGLs). When contrasted to adrenal pheochromocytoma, PGLs present the clinician with unique challenges, which include: 1) diverse location—they may be located anywhere from the tympanic membrane in the ear to the scrotum; 2) markedly variable size at detection—from 0.5 to 25 cm; 3) secretory status—sympathetic PGLs typically hypersecrete catecholamines (some uniquely secrete dopamine) and are located primarily between the mid-thorax to the pelvis; whereas, parasympathetic PGLs usually do not hypersecrete catecholamines and are located primarily between the skull base and upper mediastinum; 4) multiplicity—PGLs are frequently multiple and associated with pathogenic variants in the succinate dehydrogenase subunit genes; and, 5) increased risk of metastatic disease when compared to adrenal pheochromocytoma. These challenges will be discussed and practical clinical perspectives provided.

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PL3

Novel form of hypophysitis: New kids on the block

Yutaka Takahashi
Division of Diabetes and Endocrinology, Nara Medical University, Japan

Hypophysitis is classified according to the anatomic location of pituitary involvement and the cause (primary or secondary forms). The primary forms are characterized by an idiopathic inflammatory process confined to the pituitary gland, while the secondary forms are triggered by a definite etiology. Recently, as a secondary form of hypophysitis, an immune-mediated paraneoplastic syndrome defined as paraneoplastic autoimmune hypophysitis has been reported. This novel clinical entity, paraneoplastic autoimmune hypophysitis consists of several conditions such as anti-PIT-1 hypophysitis and a part of isolated ACTH deficiency and immune checkpoint inhibitor-related hypophysitis with common underlying mechanisms, in which an ectopic pituitary antigen expression in the complicated tumor evoked autoimmunity against pituitary-specific antigens, resulting in hypophysitis and exhibiting the injury of specific anterior pituitary cells by cytotoxic T cells. These conditions can explain at least in part, the underlying mechanisms of acquired specific pituitary hormone deficiencies. In addition, it is important to apply a comprehensive discipline of onco-immuno-endocrinology to understand the pathophysiology and this approach, the expansion and application of immune-mediated paraneoplastic syndrome to endocrine diseases may give a new clue to understand pathophysiology of the autoimmunity against endocrine organs. In this lecture, the process and lessons from the journey to encounter this novel concept will be discussed.

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PL4

The curious case of pituitary tumours

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While just a few years ago we rarely thought about genetics when looking after patients with pituitary tumours, now this aspect of endocrinology, similar to many others, is keeping the genetic labs increasingly busy. Understanding the molecular mechanisms involved in pituitary tumorigenesis and discovering the importance of the microenvironment of these tumours led to deeper understanding of pituitary tumorigenesis. Applying these new discoveries to predict tumour behaviour and to design novel therapies are the challenge what pituitary researchers are facing now. Our lab concentrated on the role of one of the genes that is associated with the development of adenomas/pituitary neuroendocrine tumours. Loss-of-function heterozygote germline mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene predispose to young-onset growth hormone- or prolactin-secreting tumours, which are often large and grow invasively. This is puzzling: why only young-onset; why only growth hormone- or prolactin-secreting tumours and why more aggressive than sporadic tumours? Using various in vitro and in vivo models, while enjoying working with skilful and talented collaborators, we attempted to answer these interesting questions. Acting as a co-chaperone, AIP interacts with the intracellular fragment of the RET receptor, activating a pathway involving PIT1 and leading to p53 accumulation and apoptosis. In one of our mouse models the pituitary-specific loss of AIP leads to abnormal pituitary development. We hypothesise that altered pituitary development may explain the strictly young-onset nature of the disease. As AIP mutation positive tumours are often large and invasive, we studied the tumour microenvironment in human and rodent samples and identified pathways leading to upregulation of pathways leading to cytokine activation and macrophage infiltration. These are just examples, how clinical observations lead to studies explaining the observed phenotype and potentially lead to better diagnostic, prognostic and therapeutic options.

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PL5

PCOS – the many faces of a disease in women and men

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Polycystic ovary syndrome (PCOS) is a common hormonal, metabolic and reproductive disorder characterized by androgen excess, ovulatory dysfunction and polycystic ovaries. The phenotypic presentation might differ between referral and unselected populations and varies within an individual over time and between individuals of different ethnic and geographic regions. Women with PCOS have increased prevalence of prediabetes and diabetes and have multiple risk factors for cardiometabolic disease and other comorbidities such as obstructive sleep apnea, endometrial cancer and mood disorders, which contribute to the health burden of the syndrome.The pathophysiology and intrinsic mechanisms underlying PCOS are complex with a strong genetic component. Earlier studies

have proposed several clinical and biochemical features for the male equivalent of PCOS, including premature baldness, increased adrenal androgen levels, insulin resistance and glucose intolerance. Even though the phenotype for male PCOS is still uncertain, available data from family studies suggest an increased risk for metabolic syndrome and type 2 diabetes in fathers and brothers of women with PCOS along with mothers and sisters. Recent studies provide evidence that PCOS-associated genetic risk for cardiometabolic disease could affect both women and men. Overall, the current name of "PCOS" might be misleading, not reflecting the complexity of the syndrome.

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Foetal and neonatal thyroid axis deficiency
PL6

Abstract unavailable

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Symposia

Spotlight on posterior pituitary

S1.1

Abstract unavailable

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S1.2

Are patients with diabetes insipidus oxytocin deficient?

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Arginine vasopressin (AVP) and oxytocin (OXT) are neuropeptides produced in hypothalamic nuclei and released into circulation from axon terminals projecting to the posterior pituitary. A disrupted hypothalamic-pituitary axis caused by inflammation, tumours, or head trauma can cause AVP deficiency, also known as central diabetes insipidus (cDI), a condition characterised by polyuria and consecutive polydipsia. Once diagnosed, desmopressin, a selective AVP receptor 2 agonist, is prescribed to overcome cDI symptoms. Despite treatment with desmopressin, patients often report residual psychological symptoms such as heightened anxiety levels, difficulties describing or expressing emotions, and depressed mood, leading to a reduced quality of life. Due to the anatomical proximity, a disrupted AVP system leading to cDI could also disturb the OXT system leading to OXT deficiency. The central oxytocinergic system is key in regulating socio-emotional functioning, including attachment and pair bonding, fear extinction, and emotion recognition. Therefore, increased psychopathological findings in patients with cDI may be caused — at least partially — by an additional OXT deficiency. However, OXT deficiency has never been proven and established as a disease entity. Few studies attempted to measure OXT in these patients and mainly focused on basal measurements delivering inconclusive results. Notably, similar to other pituitary hormones, single basal levels are unreliable in identifying a deficiency in this context and no standard provocation test for OXT has been established. Using an innovative provocation test with MDMA ('ecstasy'), our new data clearly indicate an OXT deficiency in patients with cDI, laying the groundwork for a new hypothalamic-pituitary entity. An important question, however, is whether this deficiency is related to alterations or dysfunctions in socio-emotional behaviour, which needs to be investigated in further interventional studies.

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S1.3

Tolvaptan for hyponatremia in cancer

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Hyponatremia is the most common electrolyte disorder in hospitalized patients, including cancer patients. Multiple causes can lead to hyponatremia, but frequently this electrolyte disorder is due to the syndrome of inappropriate antidiuresis (SIAD). In cancer patients this syndrome is mostly secondary to ectopic secretion of arginine vasopressin by tumoral cells. In addition, several chemotherapeutic drugs induce the release of arginine vasopressin by the hypothalamus. There is evidence that hyponatremia is associated to a more negative outcome in a number of pathologies, including cancer. Many studies have demonstrated that in different cancer types both the progressionfree survival and the overall survival are negatively affected by hyponatremia, whereas the correction of serum [Na+] has a positive effect on patients' outcome. Tolvaptan, a vasopressin receptor type 2 antagonist, has been approved more than a decade ago in Europe for the treatment of hyponatremia secondary to SIAD. Tolvaptan effectively corrects hyponatremia and the risk of overcorrection can be minimized by frequent monitoring of serum [Na+] in the 24 hours after initiation of therapy and by avoiding concurrent use of other hyponatremia treatments. Interestingly, tolvaptan has been also approved for the treatment of autosominal dominant polycystic kidney disease. In this disease tolvaptan, at higher doses than dose used for the treatment of SIAD, counteracts cystogenesis by inhibiting the cAMP/PKA pathway. This unpredicted antiproliferative effect of tolvaptan led us to hypothesize that this molecule might counteract tumor cells growth. In vitro evidence confirmed this hypothesis and in different cancer cell lines (i.e. neuroblastoma, hepatocarcinoma, small cell lung cancer, colon cancer) tolvaptan effectively reduced cell proliferation and invasiveness. These results might thus open a new scenario, in which vasopressin type 2 receptor antagonists might have a role among pharmacological strategies against cancer, in addition to their effect in correcting hyponatremia. - Hyponatremia is the most frequent electrolyte alteration in hospitalized patients; - The most frequent cause of hyponatremia in cancer patients is the Syndrome of Inappropriate Antidiuresis (SIAD); - Hyponatremia is associated with a worse outcome in cancer patients; - The vasopressin receptor type 2 antagonist tolvaptan effectively corrects hyponatremia in SIAD; - In vitro evidence indicated that tolvaptan has an unpredicted antiproliferative effects in cancer cell lines, thus possibly opening a new scenario in treatment strategies against cancer.

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Autoimmune diseases associated with Addison's disease

S2.1

Signalling in ACC pathogenesis

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Adrenocortical carcinoma (ACC) is a routinely fatal cancer with no effective treatments. Understanding the genetic landscape of ACC is essential to develop novel therapeutic strategies. Recent large-scale cancer genomics projects have revealed core signalling pathways frequently altered in human ACC tumours, including the Wnt/b-catenin pathway. Aberrant Wnt activation is a hallmark of ACC observed in ~40% of tumours, and can be driven by diverse mutational events. These include well-characterised activating mutations in CTNNB1 (b-catenin) as well as newly identified loss-of-function alterations in ZNRF3, an E3 ubiquitin ligase that promotes Wnt receptor degradation. To study the functional role of ZNRF3 loss in ACC tumourigenesis, we developed a new mouse model to specifically ablate Znrf3 in the adrenal cortex. Our studies reveal that Znrf3 loss is permissive for ACC tumour progression, but not completely sufficient. We identify ageing and sex as key extrinsic factors that cooperate with Znrf3 loss by reshaping the immune microenvironment in order to permit malignant transformation. Further, we demonstrate that sex steroid hormones are a potent regulator of the anti-tumour immune response in the adrenal. Collectively, our studies highlight the intersection between paracrine Wnt signalling and endocrine hormone signalling in the pathogenesis of ACC. These pathways have important clinical implications and may be exploited for therapeutic benefit.

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S2.2

Immune contribution to ACC pathogenesis

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The immune microenvironment plays a central but ambivalent role in tumourigenesis. During initial phases of neoplasia, both innate and adaptive immune cells recognize and destroy tumour cells. However, during the process of immunoediting, tumour cells progressively reshape the microenvironment and use immune cells to favour neoangiogenesis, tumour growth and metastasis. Until recently, the role of immune response in the pathogenesis of ACC had remained elusive. Analysis of the TCGA gene expression data had suggested that ACC were among the coldest tumours, consistent with the potent immunosuppressive action of glucocorticoids (GCs), produced locally. This was confirmed by immunohistochemical analyses showing that both CD4+ and CD8+ T cells were scarce in ACC. It further showed that tumours with highest levels of GCs were the coldest and the most aggressive. Consistent with low levels of T cells infiltration, clinical trials targeting the PD1/PD-L1 axis failed to significantly increase ACC patients' overall survival. Interestingly, analysis of a mouse model harbouring deletion of Znrf3 (the most frequent genetic alteration in ACC patients) showed that highly phagocytic MERTK+/TREM2+ macrophages, were efficiently recruited in preneoplastic lesions in male adrenals, preventing formation of aggressive tumours. In contrast, infiltration of MERTK+/TREM2+ macrophages was lower in female adrenals, allowing for tumour

progression and formation of metastatic ACC at 18 months. Analysis of TCGA data further showed that male ACC patients had generally higher levels of phagocytic macrophages signatures, correlated with better prognosis than female patients. Investigation of the mechanisms underlying this sexual dimorphism, showed that testosterone was responsible for the recruitment of phagocytic macrophages, through senescence induction. We are now investigating the downstream targets of androgens to identify factors that could be used to trigger phagocytic macrophage differentiation in ACC patients. This could constitute an exciting alternative therapeutic approach for this cancer, associated with dismal prognosis.

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S2.3

Sexual dimorphism in ACC pathogenesis

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Sex is an important parameter that influences biology and physiology of almost every organ. Sex bias is not restricted to homeostatic conditions, but is also evident in the predisposition and progression of diseases. The adrenal cortex, in particular, displays dramatic sex differences and the majority of adrenocortical diseases occur more frequently in women than in men. Understanding how sex hormones affect biology on the molecular level has therefore become an important focus, as it may help us to develop therapeutic approaches that take sex into account. In this presentation, I will provide an overview of the impact of sex on adrenal diseases. I will summarize experimental data from model systems that have revealed strikingly dimorphic expression profiles between the two sexes and demonstrated the important role of androgens in suppressing proliferation of steroidogenic cells and the recruitment of their precursors. Finally, I will highlight recent results in mouse models for adrenocortical tumors that explore the sex specific responses of the adrenal cortex to hyperactivation of the b-catenin pathway and further reveal the growth suppressing function of androgens in this disease context.

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Advances in neuroendocrine tumours – knowledge and clinical management

S3.1

Abstract unavailable

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S3.2

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S3.3

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Non-classical actions of vitamin D: What have we learned?

S4.1

Role of vitamin D in the prevention of T1 and T2 diabetes

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Since the statistical error in the RDA calculation for vitamin D has been revealed, and verified, concerns have been raised, turning the perpetual vitamin D debate groundless. Daily vitamin D up to 1000 IU <6 m, 1500 6 m-1 yr, 2500 1-3 yrs, 3000 4-8 yrs, 4000 >8 yrs are the IOM's upper tolerable limits not requiring medical supervision according to the Endocrine Society Practice Guideline Committee. The hazard ratio for all-cause mortality plateaus with 25(OH)D >50 ng/ml. 600/4000/10000 IU/day up/downregulate 162/320/1289 white blood cell genes. 4000 IU/day inhibits inflammatory hyperactivity regulating/differentiating humoral and cell-mediated immunity. T1D is the final consequence of β-cell autoimmunity but β-cell stress in T2D provokes an immune attack as well. 25(OH)D >40 ng/mL improves insulin secretion, rescues β-cells suppressing macrophage adhesion/migration and >50 ng/ml reduces T2D risk by 76%, favoring regression by 30% with no adverse events. Non-maternal T1Abs appear at 3-6 months of age with 100% lifetime T1D risk, suggesting a window for intervention during seroconversion. Primary prevention from birth with 2000 IU/day cholecalciferol reduced T1D incidence by 80% at 1 yr. T1D hits 1:300 with rising incidence increasingly affecting younger children. However, T1D has plateaued and decreased in Finland after 25(OH)D population concentrations reaching 40 ng/ml following fortification of dairy products. Screening with T1Abs at ages 2-6 yrs is sensitive but lacks a feasible preventive strategy. In a pilot clinical trial seroconversion to even multiple T1Abs was reverted within 7 m with oral calcitriol, leading to the ongoing PRECAL study (PREvention of Type 1 Diabetes with oral CALcitriol and analogues, ISRCTN17354692) with confirming results in preventing and reverting even relapses of seroconversion to T1Abs, but also to thyroid/celiac disease Abs in young children presenting early autoimmunity. Primary prevention of T1D with cholecalciferol and secondary with calcitriol/analogues seem promising, plausible, possibly cost-effective, and safe, if started well before pre-T1D, close to seroconversion.

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S4.2

Abstract unavailable

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S4.3

Randomized clinical trials with vitamin D

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Vitamin D deficiency is associated with several adverse skeletal and extra-skeletal outcomes including cancer, cardiovascular diseases, and mortality. Large randomized controlled trials (RCTs) have been conducted over the last few years with the aim to evaluate the cause-and-effect relationship of vitamin D and health outcomes. These RCTs failed to document significant effects of vitamin D on their primary outcome measures, whereas explorative analyses and meta-analyses suggest potential benefits of vitamin D regarding cancer mortality, acute respiratory infections, and asthma as well as chronic pulmonary disease exacerbations. Findings from vitamin D RCTs did not indicate significant safety concerns, except for RCTs in severely ill patients or with intermittent high-dose vitamin D treatment. Drawing final conclusions on vitamin D is, however, limited as the majority of vitamin D RCTs was not conducted in participants suffering from vitamin D deficiency and because many of these RCTs allowed for vitamin D supplementation in the placebo groups. Thus, the design of vitamin D RCTs adhered to drug RCTs and did not sufficiently account for vitamin D as a nutrient with a unique metabolism including its role as a precursor for the hormone calcitriol. Moreover, recently published RCTs did not specifically address the role of vitamin D in the prevention and treatment of rickets and osteomalacia, that remain the scientific basis for vitamin D guidelines. The learnings from the

scientific history of vitamin D with its probably overwhelming hype based on observational studies and the severe limitations of large vitamin D RCTs, that still leave us with many knowledge gaps, will hopefully inform the design of future research activities on vitamin D and other research fields.

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Prolactinomas

S5.1

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S5.2

Dopamine receptor dynamics: How to shake prolactinomas

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Prolactinomas are the most frequent pituitary tumors, and dopamine agonists (DA) are their first-choice treatment, since they normalize PRL levels and reduce tumor size in the majority of patients, by binding to dopamine receptor type 2 (DRD2) on tumoral cells. However, drug resistance occurs in a subset of patients, involving different steps following receptor activation or during the final biological responses. Although resistance to DA has been correlated with a reduced DRD2 expression, or with an altered ratio between the two isoforms of DRD2, the success of the therapy also requires the proper functioning of the machinery of signal transduction and receptor intracellular trafficking. A variety of molecules, including β-arrestins, filamin A (FLNA) and splicing factors might affect the efficacy of therapy. FLNA is a cytoskeleton actin-binding protein crucial for DRD2 expression, membrane localization and signaling. Since FLNA phosphorylation switches FLNA function from a scaffold that allows DRD2 signal transduction to a signal termination protein that hampers all DRD2 antitumoural effects in prolactinoma cells, new possible pharmacological approaches can target FLNA post-translational modification. The scaffold protein β-arrestin 2 is essential for DRD2 inhibitory effects on AKT phosphorylation with a consequent reduction of cell proliferation in prolactinoma cells. This observation not only suggest a potential role of β-arrestin 2 as a biomarker predicting prolactinoma responsiveness to treatment with DA, but also a novel pharmacological strategy based on functionally selective or biased DRD2 agonists that preferentially activate the 2-arrestin 2-mediated pathway at the expense of the canonical G-protein-mediated ones. Alternative splicing is a crucial mechanism for gene regulation, generating different functional proteins, and this process can be dysregulated in cancer. In particular, a severe dysregulation of splicing-machinery components in all the pituitary tumor subtypes compared to normal pituitaries has been observed. Somatic mutations in splicing factor3 subunitB1 (SF3B1) were found in about 20% of PRL-secreting pituitary tumors in a single paper, associated with PRL hypersecretion, increased cell proliferation and invasion. These data provide the rationale for investigating new therapeutic strategies based on SF3B1 inhibition, as well as for testing the effects of splicing alterations on DRD2 expression and responsiveness to treatment with DA. Further studies of the complex mechanisms involved in the resistance of prolactinomas to DRD2-targeted therapy could provide the basis for the development of both new prognostic biomarkers that can be used for patient selection and management and novel targets for the pharmacological treatment of these tumors.

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S5.3

Alternative medical treatments for prolactinomas

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Dopamine agonists (DA), mainly cabergoline, are nowadays recommended as the treatment of choice for patients with prolactinomas of any size to lower PRL levels, decrease tumour size, and restore gonadal function. However, some patients do not adequately respond to DA, and resistance to DA may occur in 20-30% of patients treated with bromocriptine and nearly 10-20% of those receiving cabergoline. In these patients, multimodal therapy, including surgery and/or radiotherapy, may be required. Recent evidence also supports the use of surgery as first-line therapy for patients with enclosed and not invasive prolactinomas. Aggressive and malignant prolactinomas refractory to all treatment strategies may benefit from the administration of the oral alkylating chemotherapeutic agent temozolomide, whose efficacy in terms of tumour growth control accounts for up to 50% of patients with prolactinomas. Temozolomide is nowadays recommended as first-line chemotherapy for aggressive pituitary tumours and pituitary carcinomas, following documented tumour growth. Responsiveness to temozolomide may be predicted by the evaluation of O(6)-methylguanine methyl transferase (MGMT) status by immunohistochemistry, as high MGMT expression is generally suggestive of a lack of response. The effectiveness of temozolomide has been shown to increase when combined with radiotherapy given its radio-sensitizing properties, thus offering a further therapeutic option for those individuals with aggressive or malignant prolactinomas. Aside from surgery, radiotherapy, and chemotherapy with temozolomide, alternative treatment schedules have been investigated or are nowadays tested in clinical and preclinical models, but the experience is still too scant to draw definitive conclusions. Among them, alternative hormonal treatments, cytotoxic drugs, peptide receptor radionuclide therapy, mTOR/Akt inhibitors, anti-VEGF bevacizumab, tyrosine kinase inhibitors and immunotherapy with immune checkpoint inhibitors, appeared to offer promising results. Future research will clarify the potential applications of such treatments, driving endocrinologists in the choice of the best-tailored therapy for patients with aggressive and malignant prolactinomas.

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Role of ambient temperature in human physiology

S6.1

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S6.2

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S6.3

The effect of ambient temperature on adipose tissue

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There are many effects on adipose tissue metabolism of housing mice at different temperatures. Considering the situation from a thermoregulatory perspective, it may – in retrospect – be evident that one cannot expect to observe any effect of e.g. UCP1 ablation under "normal housing" conditions. This is because at normal animal house conditions (≈20 °C), the mice experience significant cold, and they must increase their metabolism by 50-100 % (as compared to mice living at thermoneutrality) to compensate for the heat loss. This clearly means that any heat production deriving from diet-induced thermogenesis will be used in the struggle to keep up the body temperature: the mice have to produce extra heat or they will become hypothermic and die. Thus, any heat from any diet-induced thermogenesis will merely be experienced as extra heat - but if this is absent, it has to be substituted for with some other "heat". Thus, UCP1 KO mice have to

produce the same amount of heat as have wildtype mice, to survive under normal housing conditions. How this is accomplished is presently not really clarified. Under normal housing conditions, UCP1 KO do not show overt shivering (as they do when exposed to the much greater "standard" cold (=4°C). As these mice are devoid of adrenergically induced nonshivering thermogenesis, the heat must be produced in other ways, perhaps through increased muscular tone. In any case, these mice cannot allow themselves to reduce their metabolism due to the absence of UCP1: thermogenesis must be maintained, and thus there will be no "unused energy" to be stored, resulting in no obesity development under these conditions. The situation is principally very different with mice living at thermoneutrality that resembles the human situation. Here, any differences in thermogenesis (energy expenditure) should be directly observable since they are not used for thermoregulation. Mice at thermoneutrality therefore yield a fully different result. When given a high-fat diet, UCP1 KO mice become clearly more obese than the wildtype mice – although they do not develop the massive obesity seen in *ob/ob* mice.

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Aberrant/illicit expression of receptors in adrenal lesions

S7.1

GnRH in primary aldosteronism

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The mechanisms regulating aldosterone secretion in primary aldosteronism (PA) independently from the renin-angiotensin axis include diverse genetic and molecular mechanisms. One mechanism results from the activation of aberrantly expressed GPCR which are diverse and highly prevalent in adrenal tissues of patients with PA, either from aldosteronoma or bilateral adrenal hyperplasia. The levels of expression of GPCR vary greatly between different PA tissues particularly for ACTH (MC2R) and serotonin (HTR4R) receptors with local increased presence of mast cells and serotonin production in adrenocortical tissues. Transcriptome studies or *in vivo* stimulation studies have identified greatly variable expression of GnRHR or LHCGR or aldosterone response to stimuli in approximately 30% of PA patients. In some, PA became evident during pregnancy or after menopause, following activation by placental hCG or increased levels of LH after menopause. In one case, repeated episodes of severe hypertension and hypokalemia with transient PA during pregnancy was secondary to LHCGR in an aldosteronoma revealed outside of pregnancy by stimulation with HCG during 5 days and again during adrenal vein sampling. The molecular mechanisms leading to aberrant GnRHR or LHCGR are not completely elucidated. Somatic β-catenin (*CTNNB1*) mutations was suggested to induce ectopic LHCGR and GnRHR during pregnancy or menopause, but not confirmed in several patients with aldosterone response to GnRH or LH tests in vivo. More recently, overexpression of those aberrant receptors required combined mutations of *GNA11*or *GNAQ*in *CTNNB1*-mutant aldosterone-producing adenomas presenting in puberty, pregnancy or menopause. Thus, aldosterone secretion in patients with PA is not autonomous or constitutive despite the activation of aldosterone synthase by ion-channel or other genes mutations, but is dysregulated by the activation of diverse and variable aberrant expression of several GPCR by their ligands.

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S7.2

Abstract unavailable

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S7.3

LHCG Receptor in pheochromocytoma

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Pheochromocytomas/paragangliomas (PPGL) are catecholamine-producing neuroendocrine tumors that account for less than 1% of all hypertension cases. Despite their rarity, these tumors must be early detected and treated to prevent potentially life-threatening adrenergic crises. Unfortunately, PPGL are frequently unrecognized during pregnancy, leading to a high risk of either maternal or fetal complications. In return, pregnancy can trigger catecholamine secretory discharges in patients with PPGL through diverse mechanisms which are not totally understood. The observation that symptoms of catecholamine excess may occur during the first trimester of gestation suggests that pregnancy may activate the secretory activity of PPGL through the involvement of gestational hormones. We have recently reported a case of silent pheochromocytoma revealed in a pregnant woman by adrenergic myocarditis. *In vitro* studies revealed that hCG stimulated epinephrine secretion by cultured cells derived from the patient's pheochromocytoma. The tumor expressed the LHCG receptor (LHCGR), which was colocalized with catecholamine-producing enzymes. Expression of the LHCGR was also detected in an independent series of pheochromocytomas. *In silico* studies have been conducted in The Cancer Genome Atlas (TCGA) cohort and French COMETE databases which contain genomic and transcriptomic analyses of solid tumor types including PPGL. They revealed that PPGL display the highest expression levels of LHCGR mRNA among the 32 tumor types of TCGA. Interestingly, LHCGR expression level was higher in epinephrine-secreting PPGL, *i.e.* related to RET, NF1, TMEM127, MAX mutations, vs other subgroups of PPGL, and in pheochromocytomas vs paragangliomas. These data show that pregnancy can favor adrenergic crises in patients with PPGL through hCG-induced stimulation of epinephrine production by the tumors. They indicate that preconceptional diagnosis is particularly important in patients with gene mutations that predispose to epinephrine-secreting pheochromocytomas, who may experience signs of catecholamine excess as soon as the first trimester of gestation.

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GH links to cancer

S8.1

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S8.2

Lessons from Laron syndrome

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Laron syndrome (LS) is a rare genetic endocrinopathy that results from mutation or deletion of the growth hormone receptor (*GH-R*) gene. LS is the best characterized entity under the spectrum of the congenital insulin-like growth factor-1 (IGF1) deficiencies and is typically associated with dwarfism and obesity. Epidemiological studies have shown that LS patients do not develop cancer whereas heterozygous family members have a tumor prevalence similar to the general population. To identify genes and signaling pathways that are differentially expressed in LS and that may help delineate a biochemical and molecular basis for cancer protection, we conducted a genome-wide profiling of LS patients. Analyses were based on our collection of Epstein-Bar virus (EBV)-immortalized lymphoblastoid cell lines derived from LS patients, relatives and healthy controls. Bioinformatic analyses identified differences in gene

representation in a number of pathways, including apoptosis, metabolic control, cytokine biology, Jak-STAT and PI3K-AKT signaling, etc. Genes involved in positive control of cell cycle, motility, growth and oncogenic transformation are, in general, down-regulated in LS patients. These genetic events seem to have a major impact on the biological properties of LS cells, including proliferation, apoptosis, response to oxidative stress, etc. Furthermore, genomic analyses allowed us to identify novel IGF1 downstream target genes that have not been previously linked to the IGF1 signaling pathway. In summary, by '*mining*' genomic data from LS patients we were able to generate clinically-relevant information in oncology and, potentially, in other areas in which the IGF1 system is involved.

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S8.3

Lessons from experimental animal models

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Reports dating back to the 1950s have implicated human Growth Hormone (GH) in the initiation and invasive progression of several types of human cancers. A major hurdle in treating cancer is resistance to therapy. Recently, through a series of mechanistic studies using *in vitro* models and in silico analyses of human cancer patient databases, we have identified a covert role of GH in promoting cancer drug resistance via direct upregulation of: (i) the expression of ATP-binding cassette containing multi-drug transporters (ABC transporters) leading to increased drug efflux, (ii) the epithelial-to-mesenchymal transition (EMT) associated gene expression program, and (iii) the mediators of fibrosis and extracellular matrix remodeling. Additionally, based on the known effects of GH and robust expression of GHR in multiple cell types that constitute the tumor microenvironment, autocrine/paracrine GH putatively exerts potent tumor supportive actions. Therefore, we hypothesized that combining a GHR antagonist to chemotherapy can markedly improve therapeutic outcome in human cancers. Melanoma and liver cancer jointly and annually constitute $>150{,}000$ patients and $>60{,}000$ deaths respectively in the US, much due to therapy resistance. We used a syngeneic murine model of both cancers using C57BL6 mice transgenic for a GHR antagonist (GHA mice) compared to wild-type (WT) littermates, both implanted with either B16F10 melanoma or Hepa-1-6 hepatoma cells. GHA expression drastically sensitized melanoma tumors to cisplatin treatment and hepatoma tumors to sorafenib treatment. Additionally, the five-year survival rates of human pancreatic cancer and cholangiocarcinoma are a dismal 10% in 2022, indicating an urgent need for new therapeutic approaches for both these devastating diseases. For this, we used immunocompromised Nude mice for human pancreatic cancer xenografts treated $\pm$ GHA (Pegvisomant and another GHA in development in our laboratory) combined with gemcitabine. GHA markedly sensitized pancreatic cancer xenografts to gemcitabine, leading to ~40% of mice being tumor-free at the end of study. GHA similarly sensitized human cholangiocarcinoma xenografts in Nude mice to gemcitabine-cisplatin therapy. Mechanistically and in all cases, GHA led to a marked reduction in gene expression of multidrug efflux transporters, EMT markers, and fibrosis mediators. Collectively, our data provides strong pre-clinical evidence for treatment regimens combining GHR antagonism and chemotherapy leading to highly efficacious tumor clearance.

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Pitfalls in osteoporosis treatment transition

S9.1

Denosumab discontinuation

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Denosumab is an effective treatment of osteoporosis that leads to substantial increases in bone mass and clinically important reductions in fracture risk with few side effects. Most patients should continue treatment; however, some patients may need to discontinue treatment due to co-morbidities or side effects. Furthermore, some patients want to discontinue treatment because of normal or near-normal BMD and absence of fractures after years on treatment. Unlike bisphosphonates but like most other pharmacological treatments, there is no continuing effect of denosumab after discontinuing the administration. Due to the accumulation of RANKL and possibly osteoclasts during treatment with denosumab a rebound activation of bone resorption is seen in patients discontinuing denosumab after more than 1-2 years of treatment. This can partly be prevented by the administration of bisphosphonates, primarily zoledronate. The patients need frequent monitoring with p-CTX and in some cases multiple administrations of zoledronate during the first year after discontinuation in order to prevent bone loss.

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S9.2

Changing treatment within and between pharmacological classes

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Osteoporosis is characterized by decreased bone mineral density (BMD) and deterioration of bone microarchitecture increasing fracture risk. The main goal of osteoporosis treatment is preventing osteoporotic fractures. The most important predictor of treatment mediated fracture risk reduction is the increase in BMD. Treatment of osteoporosis falls into three pharmacological classes: antiresorptive agents (SERMs, oestrogen, bisphosphonates (BP), denosumab), osteo-anabolic drugs (teriparatide, abaloparatide), and dual-action drug romosozumab (mAb inhibiting sclerostin). The most commonly used are antiresorptive therapies. We switch from less potent raloxifene or ibandronate to more potent oral BPs alendronate or risedronate, or to the most potent antiresorptive drugs zoledronic acid i.v. or denosumab s.c., when more potent treatment and hip fracture prevention is needed. Namely, with raloxifene and ibandronate no significant reductions of non-vertebral or hip fractures were seen. When there are indications to discontinue denosumab a BP should be introduced. If denosumab treatment was short (1 year) an oral agent will do; after long-term treatment zoledronic acid should be applied 6 and 12 months after the last denosumab injection. In the case of treatment failure with a potent antiresorptive (significant decrease in BMD or new fractures after 12 months of adequate osteoporosis treatment) an anabolic agent is usually introduced for 24 months or dual-acting romosozumab for 12 months. It is obligatory to switch from anabolic or dual-action agent to antiresorptive agent when anabolic treatment is accomplished. In patients with very high fracture risk or those with very low BMD (T score $<$ -3 SD) at presentation the initial osteo-anabolic treatment should be introduced. Anabolic agents induce the fastest increase of BMD and reduce fracture risk more rapidly and to a greater extent than antiresorptive medications. After atypical femoral fracture or osteonecrosis of the jaw caused by long-term BPs or denosumab therapy, an osteo-anabolic agent can be introduced if no contraindications exist.

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S9.3

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The impact of paediatric obesity and its complications in adulthood

S10.1

Fatty liver in children

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Nonalcoholic fatty liver disease (NAFLD) has become the leading cause of chronic liver disease in children and adolescents in the United States, disproportionately affecting certain ethnic and racial groups. A 2 to 3-fold rise in the prevalence of obesity and overweight in children over the last 3 decades highly relates to the NAFLD epidemic. There are concerns that children with nonalcoholic steatohepatitis (NASH) are more prone to progress to cirrhosis, which may increase liver-related mortality in adulthood. Also worrisome is the recognition that cardiovascular risk and type 2 diabetes in children and adolescents are associated with fatty liver. Pediatric fatty liver disease often

displays a histologic pattern distinct from that recognized in adults. Liver biopsy remains the gold standard for diagnosis of NASH. Further pediatric-specific noninvasive biomarker development is needed to diagnose and monitor those with NASH. Targeted therapies to improve liver histology and metabolic abnormalities associated with fatty liver are needed, as unique regulatory considerations impede pediatric therapeutic trials with agents demonstrating current promise in adults. Randomized-controlled trials in children and adolescents to date show improvement in particular histologic aspects of NASH, for which vitamin E appears effective. Public health awareness and lifestyle interventions are needed to promote healthy diets, exercise, and lifestyle modifications to prevent and reduce the burden of disease.

BULLET POINTS:-

- Fatty liver disease (NAFLD) has become the most common cause of chronic liver disease in pediatric populations in developed nations.
- Certain ethnic groups such as indigenous Mexican-Americans, South Pacific Islanders, and Middle Easterners are more prone, and male gender, obesity and insulin resistance are most frequent concomitants
- The unique histologic pattern of earlier-onset NAFLD in children demonstrates a pattern of periportal steatosis and fibrosis, with relative lack of hepatocellular ballooning, in contrast to the later onset and adult pattern with panacinar steatosis, ballooning cell injury, and perivenular fibrosis.
- Limited randomized clinical controlled trials in pediatrics utilizing liver histology demonstrate utility and safety of vitamin E to improve NASH histology, while no agents have yet been proven in pediatrics to improve fibrosis.
- In order to mitigate this problem, better noninvasive tests validated in pediatric cohorts need attention, and extrapolated efficacy of drugs shown effective in adult trials need to be shown to be safe before widespread use. Until then, prevention and treatment needs to be aimed at identifying those at risk and promoting healthy lifestyle interventions.

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S10.2

Transition of obese children to adulthood

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Obesity is defined as excess body fat mass with adverse health consequences and is a chronic disease often associated with co-morbidities when it persists into adulthood. It is therefore important to support adolescents with obesity during the period of transition to adulthood in order to avoid the possible worsening of their medical condition. This risk is particularly important in the specific case of monogenic or syndromic obesities, especially as it is also a period of fragility with important psychosocial aspects. Since recently, dedicated organizations to transition have emerged such as specific platforms, to facilitate coordination between health professionals and help young people to integrate their dedicated care pathway as adult.

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Endocrine disrupting chemicals on the HPG axis at different life stages

S11.1

EDCs in precocious puberty

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Puberty is the process of physical change that occurs between childhood and adulthood, during which adolescents reach sexual maturity and become capable of reproduction. The onset and course of puberty are under the control of the neuroendocrine system. Factors affecting the timing and regulation of the functions of this system may alter the onset and course of puberty. Recent studies have demonstrated a progressive decrease in the age of onset of puberty in children around the world. Although the exact reason for this shift is not completely understood, it is generally accepted to be the outcome of a complex interaction between genetic, epigenetic, endocrine, and environmental factors. It is also known that owing to the acceleration of industrialization throughout the world, a gradual but significant increase has occurred in the number and amount of environmental pollutants. Some of these environmental pollutants are natural or synthetic chemicals with considerable effects on the endocrine system. The chemicals that have negative effects on the endocrine system are called endocrine disrupting chemicals (EDCs). EDCs exert their effects through different mechanisms: by binding to the relevant hormone receptors; by direct action on cell signaling pathways or on the central nervous system and the neuroendocrine system. Several EDCs such as phytoestrogens, topical and natural estrogens, pesticides, industrial chemicals, and phthalates have been identified as possible agents affecting pubertal development in humans. These chemicals may exert their estrogenic effects either directly by binding to estrogen receptors, increasing aromatase activity, and increasing estrogen sensitivity, or indirectly by their effect on GnRH, leading to an increase in endogenous estrogen production. In this part of the panel, the roles of EDCs in precocious puberty will be discussed with examples from animal and human studies.

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S11.2

EDCs in PCOS

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Polycystic ovary syndrome (PCOS) is now globally recognised as the most common endocrinopathy in women of reproductive age and has a prevalence of 5-21% depending on the criteria used (NIH, Rotterdam or Androgen Excess Society). What is special about the syndrome is its dual entity involving both the reproductive and metabolic profile of the women affected. As a result, any intrinsic or extrinsic factors affecting both these components, could lead to pathophysiological alterations which characterize PCOS. In fact, the heterogenicity of the syndrome suggests that apart from the genetic background, the role of the environment and lifestyle are equally important. In particular, during the last twenty years, interest has been drawn to the impact of certain environmental toxins, referred by the term 'Endocrine Disruptors' or 'Endocrine Distruptive Chemicals (EDCs)', which may modify both reproductive and metabolic pathways. Western Civilization advancement in industrial products and food processing have led to increased daily exposure to Plasticizers, such as Bisphenol A and phthalates, as well as dietary glycotoxins, such as Advanced glycation end products (AGEs), which may exert adverse effects on reproduction and metabolism throughout the female life span.

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S11.3

Role of EDCs during conception and embryo development

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Human-made chemicals have become an inevitable part of life. There are approximately 100 000 chemicals on the European market and 70% of them have not been assessed for human health risks. As a consequence, every citizen faces exposure to mixtures of poorly characterized chemicals that include, for instance, flame retardants, plasticizers, additives in personal care products, and persistent organic pollutants. The exposures correlate with multiple adverse health outcomes including infertility. My research has centred on women living in Sweden. Complex mixtures of persistent organic pollutants were found in every woman of reproductive age participating in our studies, and the levels correlated with lower ovarian reserve, longer time-to-pregnancy, and smaller chances to succeed in infertility treatments. The chemicals were present in follicular fluid at similar levels to serum, indicating direct exposure of the maturing oocytes.

Several associations were found between exposure and markers of ovarian function and fertility. For example, the concentration of the perfluoroalkyl substance PFOS in follicular fluid associated with higher basal antral follicle count but lower embryo quality in women undergoing IVF tretments. In controlled exposure experiments, PFOS disrupted gene expression and DNA methylation in bovine blastocysts at human relevant levels. Further, our *in vitro* studies with human endometrial cells showed that PFOS might also disrupt decidualization. Finally, persistent organic pollutants including PFOS were found to cross the placenta and deposit to vital organs in human foetuses. In summary, exposure to human-made chemicals is life-long and starts before birth. Epidemiological research together with experimental studies suggest multiple associations between chemicals and adverse fertility outcomes including altered oocyte maturation and embryo development. It is essential that chemical hazards towards fertility in women are better studied. Immediate actions should include development of assays that can be applied to study the safety of chemicals already in commerce, and new ones to come before they enter the market.

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Reproductive hormones in sport: When too much is never enough

S12.1

Abstract unavailable

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S12.2

Doping effects on non-reproductive organs: How the love of muscle can break a heart

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High doses of anabolic-androgenic steroids (AAS), especially when taken concomitantly with multiple other preparations, can lead to a decrease in high-density lipoprotein (HDL) cholesterol and an increase in low-density lipoprotein (LDL) cholesterol. After long-term, high-dose AAS abuse, atherosclerosis may develop, leading to coronary artery disease, cerebral vascular disease or peripheral artery disease. The degree of atherosclerosis appears to be dependent on the duration of AAS exposure. Long-term AAS users show altered electrophysiological activity of the myocardium with a significantly higher incidence of abnormal electrocardiograms after exercise. In some cases, AAS abuse resulted in a long-term elevation of blood pressure. Activation of the sympathetic autonomic nervous system, decreased parasympathetic modulation and structural cardiac changes appear to be possible causes of arterial hypertension. Some AAS in high doses cause water retention, which may be associated with arterial hypertension. AAS can cause concentric left ventricular myocardial hypertrophy, may also impair left ventricular diastolic function, which seems to be irreversible and detectable even after several years of AAS withdrawal. AAS abuse can cause a sudden cardiac death in apparently healthy young athletes. The most common causes of sudden death in young competitive athletes are hypertrophic cardiomyopathy and previously undiagnosed congenital heart failure. Other causes include coronary artery spasms, premature coronary atherosclerosis, thrombotic coronary artery occlusions due to an increased platelet aggregation and an increase in haematocrit, and direct cardiotoxic effects on cardiomyocytes.

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S12.3

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How genetics can help neuroendocrine tumor patients: from bench to bedside

S13.1

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S13.3

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In silico, in vitro, in vivo testing methods for EDC

S14.1

Development of High Throughput Screening methods for the Thyroid Hormone System

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Current strategies for identifying substances that adversely affect the thyroid hormone (TH) system (e.g. endocrine disrupting compounds [EDC]) are exclusively focussed on changes in serum TH concentrations and thyroid histopathology. This is based on the assumption that altered TH concentrations in serum directly result in impaired TH action in tissues. However, TH action is also regulated by hormone transport into cells and tissues (e.g. MCT8), activation of T4 to T3 by deiodination (DIO1-3), iodine recycling (DEHAL1), and interaction of T3 with TRs isoforms. Therefore, an analysis of EDC effects based on serum analysis and thyroid histopathology is insufficient and needs to be extended. Evaluation of the large number of chemicals for their thyroid hormone system disrupting (THSD) potential requires high-throughput screening (HTS) tests for rapid characterization of human and ecosystem hazards. In addition, a panel of reference chemicals and data describing their bioavailability and bioactivity for specific molecular targets, cellular pathways, and biological processes is needed. Such reference panels need to be validated by in vitro assays and integrated into regulatory test guidelines in order to increase confidence in the predictive value of hazard identification by in vitro methods. We developed a robust HTS platform for MCT8, DIO2, DIO3 and DEHAL1, based on the versatile Sandell-Kolthoff-Reaction to identify causal relationships for chemicals that have thyroid hormone system-mediated (adverse)effects. In total, we screened more than 40,000 compounds for each of the targets and were able to detect drugs, pesticides, and novel chemicals as potential THSD compounds. The versatile HTS platform is an ideal tool to define the causal relationships of a chemical that has thyroid hormone-dependent effects, to identify further research needs of these effects, to prioritize the multitude of substances/chemicals that should be further investigated, and to support regulatory decision making without having to resort to animal-based methods.

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S14.2

Screening of metabolism-disrupting chemicals on pancreatic β-Cells

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Diabetes prevalence has been worryingly growing in recent decades, reaching pandemic proportions. Genetic and environmental factors play a role in diabetes aetiology. While the genetic background may predispose individuals to the disease, environmental factors, including exposure to chemical pollutants that can disrupt metabolic functions (also known as metabolism disrupting chemicals or MDCs), may act as triggers to diabetes development. Despite growing evidence suggesting a relationship between exposure to MDCs and diabetes susceptibility, there is a lack of test protocols that allow the identification of MDCs with diabetogenic activity. According to the European regulation of chemicals, information on a chemical's endocrine mode of action and related adverse effects relevant for human health are required as criteria to identify MDCs. Nevertheless, there are no suitable in vitro tests for regulatory purposes that identify the potential metabolism disrupting effects of compounds. In GOLIATH, a project within the Horizon 2020 programme of the European Commission seeking to address the urgent need to develop test protocols that allow the identification of MDCs, one of our aims is to design test methods that identify MDCs that could affect β-cells. For this purpose, we used human and rat β-cell lines as well as dispersed mouse islet cells as in vitro models. We tested six chemicals at concentrations within human exposure (from 0.1 pM to 1 μM): Bisphenol-A, tributyltin, perfluorooctanoic acid, triphenylphosphate, triclosan, and dichlorodiphenyldichloroethylene. To test these chemicals, we followed an adverse outcome pathway framework, where we studied the molecular initiated event and key events, including gene expression and reactive oxygen species production. Finally, we evaluated viability and glucose-stimulated insulin secretion as adverse effects. We propose that the optimization of the test methods detailed in our study could be incorporated into a set of protocols for the identification of MDCS.

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S14.3

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Advances in reproductive endocrinology

S15.1

Effects of kisspeptin in patients with low sexual desire?

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Successful reproduction in humans at a population level, is reliant on the careful co-ordination of reproductive hormones with associated behaviours. Kisspeptin is a neuropeptide that is critical for normal hypothalamic function of the reproductive hormonal axis. However beyond its hormonal effects, non-human data suggests an emerging role for kisspeptin in a range of animal behaviours through extra-hypothalamic downstream neuroendocrine pathways. Until recently, the roles of kisspeptin in human behaviour were unknown. Investigating this through a multi-method approach employing behavioural, neuroimaging and hormonal analyses has revealed several novel neuroendocrine actions of kisspeptin in human behaviour, ultimately with clinical potential. We have shown that kisspeptin administration to healthy men enhances limbic brain activity (the main behavioural system), specifically in response to sexual stimuli. Furthermore, these changes in brain activity correlate with associated behavioural parameters such as reward, mood, and sexual aversion, providing key functional significance. In addition, attraction is a key initiator of sexual behaviour in humans and so was examined in a further study. Here, kisspeptin increases brain activity specifically in 'attraction and beauty centres' in direct response to olfactory and visual attraction cues. The next step in this series of studies was to translate these findings into patients for the first time. Hypoactive Sexual Desire Disorder (HSDD) is characterised by a deficiency of sexual desire with marked distress and affects up to 10% of men and women. Current treatment options are limited in safety and effectiveness. Kisspeptin administration to men with HSDD ($n=32$) potently increases penile tumescence (by 56%,$P=0.002$) and sexual desire ($P=0.02$), through modulations of sexual brain processing. In women with HSDD ($n=32$), kisspeptin administration increases self-reported ratings of feeling 'sexy' ($P=0.03$), with associated sexual brain processing changes. Collectively, these studies lay the foundation for future clinical applications of kisspeptin in patients with psychosexual disorders.

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S15.2

Intriguing aspects in the management of hypothalamic amenorrhea

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The proximate cause of functional hypothalamic amenorrhea (FHA) is reversible suppression of GnRH drive that results in chronic anovulation and low estradiol levels that preclude endometrial growth and shedding. Clinical management of FHA requires not only understanding the neuromodulation of GnRH drive, but also how cognitive and behavioral concomitants suppress GnRH drive. FHA results in a constellation of neuroendocrine concomitants that include activation of the hypothalamic-pituitary adrenal (HPA) axis and suppression of the HP-thyroidal (HPT) axis in addition to insufficient GnRH drive to support folliculogenesis. Hypercortisolism is the hallmark of stress and may elicit undernutrition and overnutrition depending on fuel availability, genotype, and individual factors. In monkeys and women, energy deficiency elicited by undernutrition combined with increased energy expenditure synergized with social stress to compromise ovulatory function. In monkeys, when high-fat, high-sugar food was plentiful, stressed (subordinated) female monkeys ate more than unstressed (dominant) ones and overeating was reversed by CRH antagonism. Our monkey model of stress-induced overeating may explain why obesity tracks with social stress in humans. While thin women with FHA reported attitudes such as perfectionism and high drive for thinness, attitudes associated with stress-induced overeating remain to be better characterized. The clinical management of FHA requires identifying and remediating behaviors that elicit the above constellation of neuroendocrine adaptations. Our monkey model focused on understanding the role of CRH as a modulator of GABAergic function and disordered eating. In women, we identified some of the mechanisms by which cognitive variables associated with FHA and utilized these insights to pioneer the use of cognitive behavior therapy to reverse FHA and its neuroendocrine concomitants. The neuroendocrine constellation of FHA results in antagonism of estrogen and insulin action and results in health consequences beyond reproduction compromise due to anovulation. Treatment guidelines should recognize the potential impact of FHA on pregnancy and offspring and acute and chronic compromise of cardiovascular, brain, bone, and metabolic health.

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Molecular basis of thyroid development and function

S16.1

Single cell transcriptomic analysis of zebrafish thyroid gland or thyroid organoids

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The thyroid gland regulates growth and metabolism by producing thyroid hormones in follicles composed of thyrocytes. So far, thyroid cells were thought to be a homogeneous population. To uncover genetic heterogeneity in the thyrocyte

population and to molecularly characterize the non-thyrocyte cells surrounding mature follicles or follicles in development, we have developed single-cell transcriptome atlas of mouse and human thyroid organoids derived from pluripotent stem cells and zebrafish thyroid gland. Our results identify and validate transcriptional differences within the nominally homogeneous mature thyrocyte population. Furthermore, these single-cell transcriptome analyzes identified cells that form the "niche" involved in thyrocyte development and maturation *in vivo* and in vitro, such as immune cells, fibroblasts, and cardiac cells. In addition, we identified TGF-beta as a negative regulator of thyroid maturation *in vitro*. Our study highlights the potential of molecular characterization of single cells for understanding and improving thyroid development and maturation *in vivo* and *in vitro*.

Bullets:

- Organoids
- Zebrafish
- Pluripotent stem cells
- Single cells RNAseq
- TGF beta pathway

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Research advances in adrenocortical carcinoma pathogenesis

S17.1

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S17.2

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Presenting the future of prostate cancer

S18.1

The non-coding prostate cancer genome

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Understanding the mechanisms that underly prostate cancer initiation and progression requires a comprehensive annotation of the cancer genome. While most research has focused on protein coding genes, there is increasing basic and clinical evidence that the much larger non-coding genome plays a critical role in prostate cancer tumourigenesis. The non-coding genome harbours numerous functional elements that regulate the expression of all protein-coding genes, including oncogenes and tumour suppressor. Genetic alterations to these regulatory elements can drive tumour development, progression, and response to therapy. The development and adaptation of functional genomic methodologies has allowed us to begin to annotate the non-coding genome and characterize the impact on gene expression in prostate cancer. By looking beyond only protein coding genes to the DNA that controls expression, we can gain a better understanding of how prostate cancer arises and how to effectively treat this lethal disease.

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S18.2

Cellular plasticity and neuroendocrine phenotypes in prostate cancer

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Lineage plasticity has been postulated to contribute to the failure of targeted- and immuno-therapies. In prostate cancer (PCa), the discovery that advanced metastatic castration-resistant PCa (CRPC) classified as adenocarcinoma remains fueled by the androgen receptor (AR) has ushered the development of potent AR pathway inhibitors (ARPIs), notably abiraterone and enzalutamide undoubtedly benefiting the survival of patients with advanced disease. However, a subset of patients (~20%) relapse with tumors that are no longer dependent on AR activity and, instead, activate lineage programs including stem cell and neuronal pathways. These tumors, termed treatment emergent neuroendocrine prostate cancer (tNEPC), are particularly aggressive in that no targeted therapeutic strategies exist, leading to a poor prognosis with an overall survival of only 1 year. Managing NEPC patients and developing novel therapeutic strategies have so far proven challenging due to knowledge gaps in the underlying molecular mechanisms governing tumor cell plasticity and neuroendocrine differentiation. Despite similar genetic profiles, CRPC and NEPC are distinguished by extensive transcriptional landscape rewiring. To begin addressing this, we integrated genomic, transcriptomic, epigenomic, and proteomic data that has informed us that ARPI therapy can activate a lineage switch owing to dynamic and reversible epigenetic regulations. The changes in the epigenetic landscape create an favorable environment for transcription factors to be “reprogrammed”. In particular, we uncovered new androgen receptor (AR) binding sites that allow AR to flow between alternative binding profiles and identified the neuronal determinant factor ASCL1 to facilitate phenotypic switching guided by the epigenetic modifier EZH2. This cross talk between lineage determinant transcription factors creates an opportunity to targeting EZH2 in lineage plasticity. Hence, these pre-clinical data have guided the initiation of a new arm in the Genomic Umbrella Neoadjuvant Study and other Biomarker Trials (NCT04812366) using EZH2 inhibitor.

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S18.3

Targeting androgen receptor-persistent signalling in advance prostate cancer

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Prostate cancer is the most commonly diagnosed non-cutaneous malignancy in men and a leading cause of male mortality. The androgen receptor (AR) remains the major therapeutic target with therapies that inhibit the AR signaling axis improving the outcome for patients with advanced castration-sensitive and castration-resistance prostate cancer. Despite these advances, primary and secondary resistance to AR targeting therapies is common, with evidence of ongoing AR signaling in the majority of cases. This is, in part, driven by the emergence of AR aberrations that include AR amplification, AR activating mutations, and constitutively active AR splice variants, that drive resistance to therapies targeting the AR. Nearly all currently available AR signaling axis inhibitors function through the AR ligand binding domain and have limited/no activity against AR aberrant oncogenic signaling. Therefore, the discovery and delivery of new therapeutic strategies that can block AR aberrant signaling, remains an area of unmet clinical need. Attractive strategies to overcome persistent oncogenic AR signaling include targeting AR transcription, AR RNA splicing, AR co-regulator activity, the AR N-terminus, and AR degradation, to directly impact aberrant AR activity. These approaches are currently in clinical development and undergoing evaluation in early phase clinical trials.

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Oxidative stress in thyroid disease?

S19.1

Iodine deficiency disorders

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Iodine deficiency (ID) is a public health problem and has considerable consequences other than endemic goiter, known as iodine deficiency disorders (IDD). Neonatal hypothyroidism, growth retardation, and cretenism are the results of severe ID. Neuronal migration and myelination of fetal brain requires iodine. Thus, insufficient iodine intake during pregnancy may cause permanent fetal brain damage. ID in prenatal period and early childhood has unfavorable effects on cerebral development. The duration and severity of maternal ID were suggested to be associated with worse clinical outcomes. Iodine requirement which is 150 µg/d increases toover 250 µg/d during pregnancy. On the other hand, the effect of mild-moderate ID on the long term neuromotor development of fetus is not well established. Severe ID in pregnancy is also thought to be a risk factor for pregnancy outcome, such as stillbirth , miscarriage, preterm delivery, and birth of small-for-gestational weight babies. Although ID can be easily prevented by quite inexpensive iodization strategies, it continues to be the most important cause of irreversible but also preventable mental retardation worldwide. However this strategy alone is inefficient during the pregnancy and lactation period. World Health Organization (WHO) recommends 250 µg/d iodine intake for pregnant and lactating women whereas routine supplementation programs with iodized salt provides about 100 -150 µg/d. Thus, routine iodine containing supplements are much recommended in the United States and Europe but current data indicates that it has not become much widespread.

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Update on consequences of long-term exposure/treatment with glucocorticoids

S20.1

Impairment of the HPA axis after treatment with glucocorticoids

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1% of western populations take chronic oral corticosteroids and this rises to 3% in subjects aged over 70 years old. When inhaled, topical and parenteral steroids are added to this burden, iatrogenic Cushing's becomes a major health issue. High doses of medroxyprogesterone acetate can cause glucocorticoid effects and drug interactions may impair the metabolism of some glucocorticoids (eg fluticasone), thereby increasing their potency. Patients may develop the classical features of Cushing's including growth failure, osteoporosis, myopathy and CVS risk factors all of which contribute to increased mortality. In our unpublished meta-analysis of 128 studies comprising 51,380 patients with inflammatory disease taking corticosteroid therapy, SMR was 1.84 (CI 1.27-2.41) with dose of glucocorticoid associated with higher SMR. Through the HPA feedback mechanism, iatrogenic Cushing's leads to adrenal suppression and low endogenous cortisol levels. Adrenal suppression depends upon the potency of preparation used, its dose, route and duration of administration. There are no "hard and fast rules", but adrenal suppression should be anticipated in any patient taking the equivalent of 7.5 mg prednisolone/day for over 3 weeks. The diagnosis relies on a low circulating cortisol concentration that fails to respond adequately following a short synacthen test (250 mg ACTH). Circulating ACTH concentrations may be reduced as are ACTH dependent steroids such as DHEAS. In the absence of an evidence base for management, a "treat whilst we wait" policy seems the safest way forward. Patients taking the daily equivalent of 7.5 mg prednisolone are unlikely to experience clinical features of adrenal withdrawal; however supplemental doses of steroid may be required in the event of intercurrent illness in patients taking <20 mg prednisolone/day or equivalent. Patients withdrawing from corticosteroids frequently experience fatigue, poor sleep, impaired QoL, arthralgia and have a risk of adrenal crisis. Patients should be issued with a Steroid Alert card and counselled regarding increasing steroid doses with stress/ intercurrent illness. Switching patients to tailored and more physiological doses of hydrocortisone is advocated by some. Clinical trials of selective inhibitors of 11b-HSD1 are underway in an attempt to mitigate against iatrogenic Cushings. Finally, ongoing education around surveillance, diagnosis and risk of adrenal crisis across patients and other clinical specialists is urgently required.

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S20.2

The impacts of glucocorticoids on brain outcomes and behaviour

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Critically ill patients are exposed to high levels of corticosteroids during their illness. While corticosteroid treatment has a modest effect on illness severity and survival dependent on the underlying diagnosis, observational and randomized data suggests that it also influences long-term neuropsychiatric outcomes. The mechanisms by which corticosteroid exposure during acute illness alters long-term brain function and neuropsychiatric risk are unknown. Because of the importance of the hippocampus for memory and mood and its known glucocorticoid sensitivity, we hypothesized that corticosteroid treatment during illness has long-term effects on hippocampal function in survivors. We tested this hypothesis in male and female mice using a widely used sepsis model, cecal ligation and puncture. Long-term CLP survivors exhibited anxiety-like behavior, increased central hypothalamic-pituitary-adrenal (HPA) axis activity, and persistent systemic and neuro-inflammation. Corticosterone treatment during illness primarily modified cognitive outcomes, improving non-fear memories from the time of the illness but impairing the formation of new memories. Corticosteroid-treated mice showed persistent downregulation of activity-dependent hippocampal genes suggesting a sustained decrease in hippocampal neural activity. The results suggest that corticosteroid treatment during sepsis influences hippocampal function in survivors via long-lasting changes to hippocampal activity. The relationships between gene expression, behavior, and neuroendocrine activity pointed to the importance of neural activity as well as inflammation and oxidative metabolism in functional outcomes.

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S20.3

The socioeconomic consequences of Cushing's syndrome: a nationwide cohort study

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Endogenous Cushing's syndrome (CS) causes a host of recognized physical and psychological complications, but the socioeconomic consequences of CS have not been as well-described. We recently conducted a comprehensive analysis of how patients' socioeconomic factors change before diagnosis and after treatment compared to healthy controls. In a Danish nationwide cohort, patients with CS had lower rates of employment, lower income, delayed educations, and negatively affected family lives. The negative socioeconomic trends began up to six years before the CS diagnosis was made. Both our data and previous studies indicate that socioeconomic factors show some improvement after treatment, but never fully normalize and the prognosis varies considerably by patient factors. The management of non-somatic issues in patients during their recovery phase lacks evidence-based guidance. Multiple studies have identified recurring themes of unmet patient needs. Incorporating initiatives on patient education, support groups, and specialized rehabilitation into clinical practice could address some of these issues.

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The role of muscle in metabolic diseases

S21.1

Myokines in health, resilience and disease

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The health benefits of exercise are well-recognized and are observed across multiple organ systems. These beneficial effects reduce disease risk and mortality. The molecular mechanisms that underlie the beneficial effects of exercise, however, remain poorly understood. With emergence of –omics technologies, the number of exercise-associated signalling molecules that have been identified has rapidly expanded. Signalling moieties released by skeletal muscle are defined as myokines. They can be released during acute and/or chronic exercise and exert their effects through endocrine, paracrine and/or autocrine pathways. Myokines have beneficial effects on the immune, cardiovascular, metabolic and neurological systems. However, very few of them have been shown to target adipose tissue, in particular in humans. We recently identified Growth and Differentiation factor 15 (GDF15) as a novel myokine. GDF15 is rapidly released in response to muscle contraction to promote lipolysis in human white adipose tissue. Since GDF15 has emerged as an interesting anti-obesity therapy through its central effects on appetite suppression, potential peripheral effects should not be neglected.

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S21.2

Abstract unavailable

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S21.3

The role of exosomes in clinical aspects of metabolic disease

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Extracellular vesicles (EVs) constitute a novel biological entity to identify biomarkers, and as active players in the development of liver diseases. Omics technologies have been widely applied to characterize the content and function of EVs secreted by liver cells in different pathological scenarios including drug-induced liver injury (DILI), NAFLD and metabolic syndrome. Thus, transcriptomics and proteomics of these EVs have provided several low invasive candidate biomarkers for cirrhosis in serum and urine. The transcriptomic analysis of EVs and the cells that secrete those EVs made possible the identification of a sorting RNA signal that can incorporate the RNAs into the EVs to be exported out of the cells. Another important contribution of the omics technologies to the hepatic EVs, in this case done by metabolomics has been the demonstration that hepatic EVs carry several active enzymes that are able to modify the serum metabolic composition what could have important implications for endothelial functioning. The integration of several omics technologies combined by using different experimental settings including the analysis of the cells, the EVs secreted by those cells, and the cells exposed to those EVs allow to dissect the EVs-mediated mechanisms underlying the development and progression of liver diseases and it provides novel therapeutics targets.

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Joint Sessions

Joint Session 1: ESE and EndoERN

JS1.1

Abstract unavailable
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JS1.2

Abstract unavailable
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JS1.3

Abstract unavailable
DOI: 10.1530/endoabs.90.JS1.3

JS1.4

Abstract unavailable
DOI: 10.1530/endoabs.90.JS1.4

Joint Session 2: ESE, EASO and ESPE

JS2.1

Abstract unavailable
DOI: 10.1530/endoabs.90.JS2.1

JS2.2

Abstract unavailable
DOI: 10.1530/endoabs.90.JS2.2

JS2.3

Abstract unavailable
DOI: 10.1530/endoabs.90.JS2.3

Joint Session 3: Growth Research Society (GRS)

JS3.1

Abstract unavailable
DOI: 10.1530/endoabs.90.JS3.1

JS3.2

Abstract unavailable
DOI: 10.1530/endoabs.90.JS3.2

JS3.3

Diagnosis of GHD in adults

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Adult GH deficiency (AGHD) is a common sequela in patients with pituitary or brain tumors or in patients with a history of traumatic brain injury or cranial irradiation. In addition, approximately one third of children who were diagnosed with GH deficiency will remain GH deficient as adults. Since AGHD is characterized by diminished cardiovascular health, abnormal body composition, decreased muscle strength and aerobic capacity, poor quality of life, and increased mortality, it is important to make this diagnosis and to offer appropriate GH replacement therapy to these patients. In order to do so, it is necessary to select the appropriate patients to test and to understand how to perform and interpret the panoply of tests that have been devised to make the correct diagnosis. In patients with panhypopituitarism or in adults with a history of childhood-onset GHD due to a genetic or an identified organic cause, a low serum IGF-I is sufficient to make the diagnosis of AGHD. In all other patients, a growth hormone stimulation test is required, since a single random measurement of GH, which is secreted in a pulsatile fashion, lacks precision and because a significant number of patients with AGHD will have normal levels of IGF-I. The various GH stimulation tests and the controversies regarding their interpretation will be discussed in the context of identifying those patients who are at high risk of having AGHD.

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JS3.4

Abstract unavailable

DOI: 10.1530/endoabs.90.JS3.4

JS3.5

Abstract unavailable

DOI: 10.1530/endoabs.90.JS3.5

Joint Session 4: EAA (Andrology)

JS4.1

The X chromosome and male fitness

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Male infertility affects 7% of the general population and in about 50% of cases the aetiology remains unknown. The routine genetic testing is based on karyotype analysis and the screening of Y chromosome deletions. For long time the role of the other sex chromosome, the X chromosome, in spermatogenesis remained largely unexplored. While both sex chromosomes are derived from a pair of autosomes around 300 million years ago, their current size and gene content differs dramatically. The X chromosome has remained relatively stable in magnitude with around 155 Mb, the Y chromosome decreased to around 55 Mb. The importance of the Y chromosome in male fitness is undeniable since it contains the SRY gene and other testis specific genes relevant to normal spermatogenesis. Although some earlier study predicted that the evolutionary history of the X chromosome indicates its potential specialization in male fitness, up to recently, only three genes (among them the androgen receptor gene) were considered candidate genes for male infertility. In order to provide a comprehensive picture on the role of the nearly 800 protein-coding genes on the X chromosome, we performed a large-scale screening in 2,354 azoospermic/-cryptozoospermic men from four independent cohorts. We identified a total of 55 novel genes not previously linked to male infertility. Among them 21 genes recurrently mutated and strongly associated with and 34 genes moderately associated with azoospermia/cryptozoospermia,. The most frequently affected prioritized gene, RBBP7, was found mutated in 10 men across all cohorts, and our functional studies in Drosophila support its role in germ stem cell maintenance. Collectively, this multicentre study represents a significant step towards the definition of the missing genetic etiology in idiopathic severe spermatogenic failure and significantly reduces the knowledge gap of X-linked genetic causes of azoospermia/cryptozoospermia, contributing to the development of future diagnostic gene panels.

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JS4.2

The Leydig cell biomarker INSL3 as a predictor of age-related morbidity

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Insulin-like peptide 3 (INSL3) is produced by the mature Leydig cells of the adult testes and secreted into the bloodstream in a constitutive manner, where it represents an important biomarker of Leydig cell functional capacity. It specifically activates the G-protein-coupled receptor, RXFP2, which is expressed on Leydig cells themselves, on male germ cells, and on bone cells, where INSL3 promotes healthy bone physiology. Unlike testosterone, INSL3 exhibits negligible within-individual variance, although in a population circulating INSL3 may vary by up to 10-fold between individuals. By making use of the European Male Aging Study (EMAS) cohort we investigated the relationship between circulating INSL3 and the incidence of age-dependent morbidity, in comparison with total testosterone and other HPG axis parameters. Like testosterone, INSL3 is an index of hypogonadism and consequently, after correcting for age, correlates with conditions such as diabetes, cardiovascular disease, sexual function, hypertension, bone density, and frailty. Such associations may be due to the mutual relationships not only between INSL3 and testosterone, but also with BMI, or smoking. However, when multiple regression analysis was used to assess such relationships between morbidity in the second phase of the EMAS study and either INSL3 or testosterone in the same individuals in the first phase of the study, with blood samples collected 4 to 5 years previously, then INSL3 was significantly and independently predictive for 6 of the conditions later assessed, whereas testosterone was predictive for only 3 of these. Because of its low within-individual (though high between-individual) variance, even over long periods of time (several years at least), circulating INSL3 is an excellent biomarker for possible hypogonadism and dependent future conditions. Our current research is investigating the mechanisms behind these relationships and addressing the question why some individual men may have high or low INSL3 throughout their adult lives.

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JS4.3

Abstract unavailable

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Joint Session 5: ESE, SBEM, FASEN and SMNE

JS5.1

Obesity and metabolic syndrome in Type 1 Diabetes

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In recent years there has been an increase in the incidence and prevalence of overweight and obesity around the world. Overweight and obesity are more common among people living with type 1 diabetes (T1D) than originally anticipated[1] . The SEARCH study found 21% of T1D patients are overweight[2] and 12.6%[3] are obese. The T1D Exchange Study found an obesity rate of 13.1% in adolescents[4] . The DCCT-EDIC Study found that the obesity prevalence, in the intensive treatment arm, increased from 1% at baseline in the DCCT to 31% at 12 years follow-up of EDIC[5] . RENACED-DT1 found 42.4% of overweight and 8.1% of obesity in Mexican patients with T1D[6] . Updated results (2022) will be presented during the meeting on the prevalence of obesity for the overall population and for T1D patients for Belgium, Kuwait and Mexico. Risk factors for overweight and obesity include non-physiological insulin administration route (subcutaneous), decrease in exercise due to hypoglycemia fear, excessive carbohydrate intake secondary to hypoglycemia, and hormonal changes[1] . Obesity increases the risk of cardiovascular disease. In people living with T1D it is difficult to quantify the degree of insulin resistance (IR). Those using >1 IU of insulin/kg/day are considered IR. IR and metabolic syndrome can also be calculated by the estimated glucose disposal rate eGDR (7), that takes into account the waist to hip ratio, presence or absence of hypertension and HbA1c. Patients with eGDR $<$ 7.5 mg/kg/min are considered IR[7] . Drugs used for type 2 diabetes treatment have been studied in T1D and have demonstrated decrease in weight and slight improvement in metabolic control in T1D subjects but are not approved for their use. It is imperative to address, prevent and find treatments for obesity in T1D.

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JS5.2

Testosterone replacement in metabolic disorders. To give or not to give

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Several studies have shown that men with obesity, insulin resistance, prediabetes, and type 2 diabetes mellitus (DM2) have significantly lower testosterone (T) levels and a higher prevalence of hypogonadism than men with normal metabolic status. It is estimated that between 30 and 40% of men with T2DM have low levels of T, assessed as total T, free T, or bioavailable T. But, as part of the integrative metabolic system, testosterone has insulin-sensitizing hormone properties through several mechanisms. So, the metabolic state and the reproductive axis are normally in a balance of mutual convenience. In that sense, while low T is a risk factor for a future metabolic condition, any metabolic condition is a risk factor for developing low T. I will discuss the evidence for the utility of testosterone replacement therapy in hypogonadal men to improve metabolic status. In men undergoing treatment with changes to healthier habits, does the addition of exogenous T improve the results of these treatments?

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JS5.3

Abstract unavailable

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EYES Symposium

EYES1.1

Abstract unavailable

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EYES1.2

Obesity fuels prostate cancer: A source of diagnostic biomarkers and therapeutic targets

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In the last years, obesity, and its associated metabolic comorbidities, have been proposed as risk factors for prostate cancer (PCa) development and linked to a more aggressive disease (e.g., PCa with poor prognosis, shorter time to develop biochemical recurrence and metastasis, and associated with increased mortality). In this sense, PCa represents the most common cancer-type in developed countries among men and it is one of the leading causes of cancer-related deaths in this collective, representing a major health problem worldwide. Unfortunately, early detection and clinical management of PCa face severe limitations. Currently, PCa initial diagnosis is mainly based on plasma prostate specific antigen (PSA) levels, a biomarker that exhibits profound drawbacks (i.e., poor specificity and predictive value). Particularly, when plasma PSA levels range between 3-10 ng/ml, also known as “grey zone”, the sensitivity, specificity, and predictive capacity of PSA is significantly worsened. Consequently, a high number of biopsies are required to detect the tumors, reducing patient quality of life. Likewise, clinical management of advanced PCa also faces major limitations, including the development of resistance to hormonal (i.e., AR pathway inhibitors) and chemical therapies (e.g., taxanes). Hence, new non-invasive and personalized diagnostic/prognostic biomarkers, as well as more effective therapeutic tools for PCa are urgently needed. In line with this idea, the endocrine/metabolic alterations that occur under an obesity state, impact normal prostate gland function; however, the precise mechanisms involved in the pathological association between obesity and cancer are still not fully elucidated. In this context, recent studies from our and other groups have demonstrated that factors belonging to different endocrine/metabolic systems (e.g., ghrelin axis, adipokines) as well as molecular components involved in the regulation of the transcriptome (e.g., miRNome, splicing machinery) are significantly altered in PCa samples, which might be useful as diagnostic/prognostic biomarkers and therapeutic targets (particularly under obesity conditions).

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EYES1.3

Abstract unavailable

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ECAS Symposium

ECAS1.1

Abstract unavailable
DOI: 10.1530/endoabs.90.ECAS1.1

ECAS1.2

Abstract unavailable
DOI: 10.1530/endoabs.90.ECAS1.2

ECAS1.3

Abstract unavailable
DOI: 10.1530/endoabs.90.ECAS1.3

ECAS1.4

Abstract unavailable
DOI: 10.1530/endoabs.90.ECAS1.4

New Scientific Approaches

Single cell-omics approaches
NSA1

Abstract unavailable

DOI: 10.1530/endoabs.90.NSA1

Effects of thyroid in organoid models
NSA2

Abstract unavailable

DOI: 10.1530/endoabs.90.NSA2

Circulating DNA to identify targetable mutation in metastatic endocrine cancers
NSA3

Circulating DNA to identify targetable mutation in metastatic endocrine cancers

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Pheochromocytomas or Paragangliomas (PPGLs) are catecholamine-producing tumors with a 15% to 20% risk of developing metastasis, which is related to poor prognosis and shorter survival. Despite PPGL metastasis can present an indolent course for years, it eventually progresses leading to the death of the patient. As is usually the case for rare tumors, drug development for PPGL has been very slow and there are currently no effective therapies for progressive PPGL metastasis. We here applied a circulating tumor DNA (ctDNA)-based approach to a) assess the prognostic value of the levels of ctDNA analyses, b) to characterize the genomic landscape of metastatic PPGLs, and c) to identify potential therapeutic targets that can guide personalized treatments to the patients. We will present the results of our ctDNA-based analysis in a large cohort of metastatic PPGLs from an international consortium composed of groups from the ENSAT and A5 Networks, and other groups.

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Debate Sessions

Should diabetes insipidus be re-named?

D1.1

Pro: Should diabetes insipidus be re-named?

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All those involved in delivery of health care are obliged to deliver safe and effective management for patients. Effectiveness is often achieved where specialists for the condition are involved. In contrast, patient-safety depends of recognition of the condition in question and then use of appropriate treatment and management, regardless of who is seeing the patient. This is particularly the case where there may be a rare disease confused for a common one, and where the treatments needed are completely different. It is in this scenario that there is**an absolute need to rename the condition formally known as 'diabetes insipidus'**. Patients with this condition may present to the generalist and be confused with patients who have **'diabetes mellitus'**, with reports for some of desmopressin not being made available or not being given resulting in life-threatening dehydration, and for others having frequent glucose finger prick testing when it was not needed. Whilst the word 'diabetes' is time-honoured being first used around 250-300 BC and is derived from Greek meaning 'syphon – to pass through', it has no place in the 21st century as a descriptor for the pathophysiological condition of **'AVP deficiency or resistance'**; the continued use of 'diabetes insipidus' perseverates patient risk. and for this reason its use must be abandoned. There are precedents for name change in medicine, and although this takes time and effort to achieve, the end goal of enhancing patient safety justifies the endeavour!

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D1.2

Con: Should diabetes insipidus be re-named?

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Recently, a position statement of a working group for renaming diabetes insipidus (DI) appeared in several renowned endocrine journals aiming to promote a change in the established name of DI. According to this position statement, the major arguments for renaming DI are: (a) it does not optimally reflect the underlying pathophysiology (b) it is often confused with diabetes mellitus (DM) leading to treatment errors and consequent adverse outcomes for patients. Although the above arguments sound reasonable there are still good reasons against changing the name of DI. Diabetes insipidus is a well-established medical term that has been in use for many years. The term "diabetes" runs deep in history and elegantly and accurately describes polyuria which is the hallmark symptom in all patients with DI. On the other hand, nowadays only a proportion of DM patients suffer from polyuria, while even more inappropriate is the use of terms like "pre-diabetes". So, renaming DI and maintaining DM does not sound a choice which optimally reflects the underlying pathophysiology and clinical presentation of these disorders. What is true, for both health care providers and patients, is that the real need to change the name of a rare disease like DI, is its potential confusion with a very common disease like DM. However, is it certain that renaming DI will solve the existing problems? Owing to its rarity, DI is often neglected by health-care professionals, and increased awareness of this disease is urgently needed. In line with this, non-availability of desmopressin has been noticed in many emergency situations and obviously this is not going to be corrected by renaming DI. Also, a substantial proportion of patients with central DI suffer from additional anterior pituitary hormone deficits which if neglected are equally detrimental for the patients. So, renaming DI can only partly improve a situation for which the major challenge is to increase awareness and improve education and upskilling of healthcare workforce, to avoid serious untoward events during the emergency care of these rare patients. It should also be noticed that changing the name of DI would likely create problems with statistical reporting and library database searching, while the suggested use of both names for some years from now-on will add more complexity for both patients and non-aware healthcare providers. In conclusion, like for most rare diseases it may be more productive to focus on improving patient care and finding better ways of management, rather than changing its name.

DOI: 10.1530/endoabs.90.D1.2

Testosterone supplementation for the aging male: curse or blessing?

D2.1

Abstract unavailable

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D2.2

Abstract unavailable

DOI: 10.1530/endoabs.90.D2.2

Should patients with adrenal incidentaloma and autonomous cortisol secretion be treated with surgery?

D3.1

Pro: Should patients with adrenal incidentaloma and autonomous cortisol secretion be treated with surgery?

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Adrenal incidentalomas (AI) are recognized more and more frequently, due to the widespread use of CT. Although unexpected, these tumors raise the question of a putative morbidity related either to their proliferation potential or to their endocrine secretion. Regarding proliferation it is now established that a low (<10 UH) and homogeneous density on unenhanced CT scan is specific for a benign adrenocortical adenoma, which do not need to be operated for fear that they may become malignant. Regarding secretion some patients may have previously unrecognized overt Cushing's syndrome (CS) and should be operated. By contrast there is a debate regarding patients with no overt CS, but an autonomous secretion of cortisol (ASC), defined by plasma cortisol level >50 nmol/l after 1 mg dexamethasone-suppression.

We will argue here that many of these patients should also benefit from surgery, based on the following points:

- There is good evidence for an association of ASC with diabetes, hypertension, and an increased mortality, both cardiovascular and global.
- Several retrospective studies reported that patients with ASC who were operated showed improvement of hypertension and metabolic control.
- One recent prospective randomized controlled study demonstrated improvement of hypertension and metabolic control and the promising results of another larger randomized control are expected soon.
- A meta-analysis of laparoscopic unilateral adrenalectomy has reported no mortality and very little morbidity: for AI with ASC there may be transient adrenal insufficiency, related to the previous hypothalamic/pituitary suppression by ASC, but this must be understood as another proof that ASC does have significant clinical effect.
- The cost of surgery is considerably lower than the alternative of a life-long medical anticortisolic treatment.

We believe that these points should lead us to perform adrenalectomy in most patients with AI and confirmed ASC who do not have specific risks for surgery and who accept it.

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D3.2

Con: Should patients with adrenal incidentaloma and autonomous cortisol secretion be treated with surgery?

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Background
Adrenocortical carcinoma (ACC) is a rare cancer associated with hereditary syndromes in 10% of cases. However, data on germline variants (GVs) in adult patients with sporadic ACC are limited.
Methods
We analyzed germline DNA from 150 adult patients with sporadic ACC sequentially referred to our centers between 1998-2019. We designed a custom panel of 17 genes potentially involved in the pathogenesis of ACC: AIP, APC, ARMC5, ARNT, BRCA1, BRCA2, CTNNB1, IGF2, MEN1, MSH2, MSH6, PDE8B, PDE11A, PRKACA, PRKACB, PRKAR1A, and TP53. NGS data were analyzed by a semi-automated bioinformatic pipeline. All GVs were studied using effect predictor tools (PolyPhen and SIFT). Specific databases (ClinVar, Varsome, gnomAD, IARC TP53, HGMD) were used for variant classification according to ACMG criteria. Variants interpreted as pathogenic (P) or likely pathogenic (LP) were considered as positive. Clinical, pathological and genomic data were analyzed in different Cox models to study prognostic impact of covariates for disease-free survival (DFS), progression-free survival (PFS) and overall survival (OS).
Results
We identified 21 unique GVs in in 9 genes including APC ($n=3$), ARMC5 ($n=3$), MSH2 ($n=3$), PDE11A ($n=3$), TP53 ($n=3$), MSH6 ($n=2$), PDE8B ($n=2$), AIP ($n=1$) and CTNNB1 ($n=1$). Eleven positive GVs were found in 14/150 patients (9.3%). We found a new GV in TP53 (G105D) in a patient who was later found to have a sister with ACC and, for the first time, 3 GVs in ARMC5 (P731R). Patients with ARMC5 GVs had large cortisol-secreting tumors and one case displayed combined pathologic features of ACC and macronodular cortical disease. Positive GVs were associated with a shorter OS (50 vs 142 months, HR 1.81; 95%CI, 0.86-3.82,$P=0.118$) and PFS (8 vs 30 months, HR 3.11; 95%CI, 1.57-6.16,$P=0.001$) but not DFS (27 vs 32 months, HR 1.07; 95%CI, 0.52-2.22,$P=0.845$). At multivariate analysis, known clinical factors (age, surgery of primary ACC, ENSAT stage, hypercortisolism) were found to have prognostic impact on OS. However, GVs remained independent predictors of PFS and OS in metastatic patients.
Conclusions
In a series of 150 patients with ACC, we found that 9.3% of them had positive GVs. We describe for the first time the presence of ARMC5 GVs in patients with ACC and we found a novel pathogenic variant of TP53. Pathologic features of one ARMC5 case suggest a possible progression from macronodular adrenal hyperplasia to ACC. Finally, the present findings suggest that GVs can affect ACC progression and survival of affected patients.

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Meet the Expert Basic Scientist Sessions

MTEBS1

How can we use human organoids in EDCs research?

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The pathophysiology of human neurodevelopment entails complex interactions between individual genetic backgrounds and environmental exposures. Endocrine Disruptive Chemicals (EDCs), a heterogeneous class of compounds widely present in our environment, can interfere with human endocrine system and the effects of this exposure on the developing brain can cause adverse neurodevelopmental effects. As opposed to previous works focusing on single compounds, we studied an EDC mixture associated to language delay in a longitudinal pregnancy cohort study. We integrated the epidemiological results with in vitro molecular testing on human fetal neural progenitors, and cortical brain organoids (CBO). Transcriptomic analysis revealed that chronic exposure to the mixture altered genes related to epigenetic regulation, cell proliferation, and neuronal maturation. Moreover it down-regulated bona fide ASD-causing genes (annotated with the highest scores in the Simons Foundation Autism Research Initiative (SFARI) gene database), thus indicating that EDC exposure interferes with the same molecular targets implicated in the pathogenesis of ASD cases caused by genetic mutations. Experimental results were then used to determine that up to 54% of the investigated women exceeded exposure levels of concern, emphasizing the need to take mixtures into account for chemical testing, and providing an integrative framework to guide risk assessment (1). Building on that, we are deepening our investigation of causal links between endocrine pathways alteration and developmental neurotoxicity in the ENDpoiNTs project (https://endpoints.eu/), where we systematically exposed CBO to single compounds and mixtures of several hormones and EDCs, thus establishing a molecular and cellular atlas of endocrine impact on the developing human brain cortex. We also established a novel experimental platform to carry out high throughput developmental disease modelling and EDC exposure on CBO. We implemented and benchmarked a new strategy to multiplex CBO from multiple induced pluripotent stem cell lines (generating mosaic CBO), and leveraged single cell transcriptomics to deconvolve individual cell identity-using variant calling. We thus integrated our longitudinal (up to day 300 CBO) single cell datasets, where all the relevant clusters of neurodevelopmental cell populations were annotated and analysed, and we deeply characterised specific neuronal (excitatory and inhibitory lineages) and glial developmental trajectories. This work represents a unique resource for using brain organoids to perform disease modelling at scale, towards an in vitro epidemiology paradigm, for neurotoxicological studies on multiple genetic backgrounds.

DOI: 10.1530/endoabs.90.MTEBS1

Identifying new receptors in the regulation of fertility
MTEBS2

Abstract unavailable

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New treatments in hypopara from lab bench to bedside
MTEBS3

Abstract unavailable

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Meet the Expert Sessions

MTE1

Lipodystrophies: Are they really rare?

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Lipodystrophy is a rare disease characterized by generalized or partial lack of adipose tissue. Lipodystrophy is associated with leptin deficiency and leads to severe insulin resistance and metabolic abnormalities. A previous literature review reported an estimated prevalence of less than one in a million based on the assumption that only one-fourth of the patients with lipodystrophy may have been reported. Later, the prevalence of lipodystrophy was estimated through a search of electronic medical records that revealed a prevalence of 1.3–4.7 cases/million. The prevalence of lipodystrophy in Europe was reported as 2.63 cases/million (0.96 and 1.67 cases/million for generalized and partial lipodystrophy, respectively). In contrast to previous estimates, a recent study in the United States (US), using large clinical cohorts, reported an estimated clinical prevalence of lipodystrophy disorders of 1 in 20,000 individuals, with an estimated genetic prevalence of disease of ~1 in 7,000 in the general population. In this session, we will shortly review the natural history of lipodystrophy and try to understand why lipodystrophy is an underdiagnosed condition and many patients with lipodystrophy experience a long journey to diagnosis. We will look at specific subtypes of lipodystrophy which create a real diagnostic challenge. We will also have a deeper look at the recent US prevalence study and discuss the possibility of overestimation of the prevalence of lipodystrophy based on the methodology used. Finally, we will explore innovative ways of diagnosing lipodystrophy and overview basic tips that can help overcome this diagnostic challenge.

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Glucocorticoids and obesity

MTE2

Identifying new receptors in the regulation of fertility

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Inhibins and activins were discovered based on their abilities to inhibit and stimulate follicle-stimulating hormone (FSH) secretion from pituitary gonadotrope cells. These ligands are members of the TGFbeta superfamily of secreted ligands. Current dogma suggests that activin B produced by gonadotropes stimulates FSH production in an autocrine/paracrine manner. Inhibins A and B from the gonads suppress FSH by competing for binding to activin receptors. This binding is aided by the co-receptor betaglycan. Recent research from our lab challenges elements of this model. First, inhibins A and B use distinct co-receptors in gonadotropes to suppress FSH. The newly discovered inhibin B co-receptor, TGFBR3L, may be a new drug target to regulate FSH levels. Second, activin B is dispensable for FSH production. Rather, another TGFbeta ligand, myostatin, which is produced in skeletal muscle, is the main driver of FSH synthesis. Myostatin shares properties with activins, including some receptors and soluble binding proteins. This explains, in part, the misattribution of activin action in FSH regulation. We will discuss the clinical significance of these findings.

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MTE3

New medical treatments for Graves' orbitopathy new guideline on immunological treatments

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Graves' orbitopathy (GO) affects 20-40% of patients with Graves' disease. Some patients require several treatment modalities with outcomes that are often far from ideal. The quest for disrupting the autoimmune process with targeted therapies began with the emergence of biologics developed for rheumatoid arthritis. In the meantime basic research revealed an important potential role for cross-talk between the TSH and IGF-1 receptors on orbital fibroblasts. This attracted commercial interest, which steamrolled a monoclonal antibody into the GO therapeutic arena. Teprotumumab, an IGF-1 receptor blocker and a failed anti-cancer drug, was revived and repurposed. Thus a new era was born, unveiling unprecedented efficacy in GO including reduction in proptosis and resolution of diplopia. But this came with significant baggage. Unexpected side-effects, a significant relapse rate and an extraordinary high cost. Clinicians in the USA (the only country where the drug is licensed presently) have embraced it and seem to use it widely including for patients with characteristics that were exclusionary in the clinical trials that led to FDA approval. The commercial success of teprotumumab has stimulated interest in the drug development industry and currently several trials are underway in a race to bring competitors to the market. This is good news for patients with GO, but the soaring costs are a concern. The teprotumumab paradigm brings to the forefront two important questions: do endocrinologists have the power to prevent the emergence of GO among their patients with Graves' disease and bypass the need for astronomically expensive treatments? Do professional organisations have a role in curtailing the greed of the pharmaceutical industry? There is ground to argue that the answer to both questions is yes. Recent guidance from the European and American Thyroid Associations joint Consensus Statement and from the European Group on Graves' Orbitopathy have provided their valuable perspectives.

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World Health Organization new classification of endocrine tumors (WHO 2022): What's new in neuroendocrine neoplasms?

MTE4

Abstract unavailable

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Personalised treatment of diabetes emergencies

MTE5

Abstract unavailable

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Role of EDCs in lactation

MTE6

Abstract unavailable

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Transition of an adolescent with hypopituitarism

MTE7

Abstract unavailable

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Osteoporosis in women with hypothalamic amenorrhea, diagnosis and management

MTE8

Abstract unavailable

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MTE9

Pituitary dysfunction in trauma

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The leading causes of TBI which may result in pituitary dysfunction are car accidents, falls, sports-related head injuries, violence and war accidents. The prevalence of pituitary dysfunction is approximately 15% following TBI. GH is the most common hormone lost after TBI, followed by gonadotropins (FSH and LH), ACTH and TSH. The proposed pathophysiological mechanisms responsible for the development of pituitary dysfunction after TBI include sella turcica fractures, genetic predisposition, autoimmunity, ischemic changes, hypoxia, increased intracranial pressure, diffuse axonal injury, and persistent neuroinflammation. Recent studies revealed that pituitary dysfunction may also occur in athletes dealing with combative sports including boxing, kickboxing and football. These types of sports are characterized by chronic repetitive head trauma and they are accepted as mild TBI (mTBI) or concussion. The pituitary volume on MRI in retired boxers with hypopituitarism is significantly lower when compared to the boxers with normal pituitary function and healthy subjects. Pituitary dysfunction in TBI victims including athletes may occur during acute phase just after head trauma, it may improve with time or new deficiencies may develop during follow-up. Severity of TBI, patients demographics, radiologic abnormalities and hypopituitarism, ACTH deficiency in particular during acute phase are the risk factors for TBI-induced pituitary dysfunction. Cortisol, thyroid hormone and AVP deficiencies should be investigated during early phase after TBI and screening of gonadotropins and GH is recommended to be delayed 6 to 12 months following TBI. Hypopituitarism may be very easily overlooked because of non-specific or mild symptoms at least in some patients. For this reason, the great majority of the patients suffered from TBI remain undiagnosed and untreated. We recommend an approach to the diagnosis of pituitary dysfunction in the patients with head injury history in routine clinical practice. Treatment of hypopituitarism due to TBI is the appropriate replacement of deficient hormones.

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MTE10

Advantages and disadvantages of surgery, radioactive iodine, and long-term anti-thyroid drug therapy for Graves' hyperthyroidism

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Graves' disease (GD) is an autoimmune thyroid disorder being the most frequent cause of hyperthyroidism in iodine-sufficient countries. There are three main ways to treat GD: pharmacotherapy, radioiodine treatment (RAI) and thyroidectomy. During the lecture certain advantages and disadvantages of those three methods will be discussed. Advantages of anti-thyroid drugs (ATDs) include their immunosuppressive action and outpatient therapy. Disadvantages are higher relapse rate (about 50%, especially in younger patients, with large goiter, and higher free thyroid hormones), long duration of therapy, side effects (about 13%) and lack of histopathological verification if concomitant focal lesions occur. Benefits of RAI is lower risk of relapse (about 15%), outpatient therapy, no need for hospitalization or anesthesia. It is a good option for older patients, with contraindications for surgery. Weaknesses include the need for following radiation safety procedures, the risk of increase in TRAb level following therapy and thus exacerbation of orbitopathy, lack of histopathological verification if concomitant focal lesions occur, and often is associated with the need for lifelong L-thyroxine substitution. Pros of surgery are histopathological verification of concomitant lesions, lower risk of relapse (about 10%), decrease of TRAb level, lower risk of orbitopathy exacerbation. It is a good option for patients with large or nodular goiter as well as for patients who want to achieve stable euthyroidism quickly. Cons of surgery are the need for hospitalization and anesthesia and longer reconvalescence. Treatment of GD may be associated with side effects or cause permanent damage to the thyroid gland and the need for hormonal treatment for the rest of patients' life. Thus, at each stage of the therapeutic process, an objective judgment made by the physician, taking into account the needs and preferences of the patient, as well as the available diagnostic and therapeutic methods, is necessary.

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MTE11

Menopause and adrenal incidentalomas - a distinct endocrine association

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Adrenal incidentalomas (AIs) are tumours accidentally detected by various imaging methods applied without suspecting adrenal pathology, indicating that most of them are nonfunctional. The most frequent hormonal alteration in AIs is autonomous cortisol secretion (ACS), a condition of altered hypothalamic-pituitary-adrenal axis activity, established on the biochemical parameters of hypercortisolism, without phenotype expression of Cushing's syndrome. Since mild hypercortisolism is associated with metabolic complications such as abdominal obesity, insulin resistance, hyperglycemia, atherogenic dyslipidemia, and hypertension, which are a cluster of the metabolic syndrome, thenew term 'metabolic autonomous cortisol syndrome' (MACS) has been suggestedfor this condition.The prevalence of AIs ranges from 3% in 50-year-old patients up to 10% in the elderly. Depending on the applied diagnostic criteria, the prevalence of ACS in patients with AIs is estimated at 5-30%. Given that the overall prevalence of ACS is up to 2%, a significant part of the population may have MACS comorbidities. Postmenopausal aging is accompanied by an unfavorable change in body composition towards an increase in abdominal adiposity. Consequently, this is associated with greater lipolytic activity and inflammation, resulting in the onset or deterioration of cardiometabolic complications. Studies on the influence of regional fat distribution suggest that preservation of gluteo-femoral subcutaneous adipose tissue, independently of the presence of abdominal obesity, could have beneficial effects on insulin sensitivity, and the glucose and lipid metabolism. Regardless of the degree of cortisolemia in postmenopausal women with AIs, tissue specific glucocorticoid sensitivity may influence body composition as well as metabolic parameters determining the individual predisposition for the development of MACS. Chronic mild hypercortisolism is associated with an increased risk of osteoporosis and fragility fractures, but glucocorticoid receptor gene polymorphism may modulate skeletal sensitivity to the glucocorticoid excess.

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Adrenal e-consultations

MTE12

Abstract unavailable

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Nurse Sessions

Acromegaly: Technologies and therapies

N1.1

Abstract unavailable

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N1.2

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N1.3

Case Study: Complex case of acromegaly

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Presenting the complex journey of a 36 year old lady who following over 2 years of symptoms was found to have raised IGF1 and prolactin. She had microscopic transsphenoidal resection of pituitary adenoma. This was followed by different medical therapies and Gamma knife radiotherapy. She was also referred to many other specialists for Acromegaly related conditions and surveillance. The pathway to diagnosis can be full of barriers and may take many years for a patient to travel along. It is not only medical and surgical interventions a patient needs but psychosocial care and support as well. The Endocrine Specialist Nurse is often the only consistent link for a patient with Acromegaly on what is often a challenging journey.

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Hypogonadism: Causes, consequences, consensus and controversies

N2.1

Abstract unavailable

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N2.2

Consequences: Hypogonadism and sexual dysfunction, Hypogonadism and bone health, Hypogonadism and anaemia, Hypogonadism and cardiovascular risk

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Testosterone (T) declines with ageing and chronic diseases, including obesity and metabolic conditions. This results in T levels in the hypogonadal range in up to 15% of middle-aged elderly men from European general population. These are at risk to develop the clinical consequences of decreased T. Low T is associated with reduced sexual desire, erectile dysfunction and orgasmic impairment. Restoring T levels using T replacement therapy is able to improve the symptoms. However, it is pivotal to understand that not only low T but also ageing and comorbidities have a role in inducing sexual dysfunction. Therefore, a careful assessment is necessary to discern the underlying risk factors and to decide the appropriate treatment. In fact, particularly for erectile dysfunction, the benefits of T therapy are eroded by the detrimental effect of metabolic disorders. Men with low T are at higher risk for cardiovascular events. The underlying mechanisms are deemed to be multiple and only partially known. Whether the treatment is beneficial is still unclear and some data suggest that it may be even detrimental. In the last decade, several studies have been published showing an association between T treatment and adverse cardiovascular outcomes. However, these studies have been criticized for several flaws. Current evidence form meta-analyses suggest a neutral effect of T treatment on cardiovascular events. A known consequence of low T reduced bone mass and osteoporosis. T therapy is able to restore bone mass. However, data showing that T treatment is able to reduce risk of bone fractures are currently lacking.

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N2.3

Abstract unavailable

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N2.4

Abstract unavailable

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Clinical workshop for nurses

N3.1

Testosterone Replacement Therapy: Overview

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The interest in replacing testosterone, the most important male hormone, dates to back to antiquity. Ancient Roman and later in the Middle Ages European, Arabic and Chinese physicians prescribed the ingestion of animal testes to restore male virility. Fast forward through an interesting and questionable history of organotherapy that includes various concoctions of questionable sources for xenotransplantation of testes to modern attempts to replace testosterone. Modern testosterone therapy includes formulations administered by various means. Injectable testosterone therapy has been available for decades and has historically been given IM. A 2022 trial suggests that similar pharmacokinetics and mean serum testosterone levels can be achieved using subcutaneous injections, making self-administration easier. Buccal patches placed on the gums also delivers controlled release testosterone directly into the systemic circulation, bypassing first-pass hepatic metabolism and increasing bioavailability. Nasal testosterone has been available in the US since 2014 and EU since 2020 for treatment of low testosterone. Transdermal administration includes gels, liquids and patches. The first patch became available in the 1980s and was placed on shaved scrotum. A 2020 Dutch study followed 12 men for 4 years and found 7 of 12 men found this an acceptable therapy. A more acceptable patch is placed in any of several locations, but not the scrotum. Gels are applied to specified areas defined by the manufacturer. Subdermal pellets were first developed in the 1940s and surgically placed in the hip area or other fatty tissue. Oral replacement has met with difficulties of poor absorption and liver toxicity. Testosterone undecanoate became available in oral formulation in the EU in the 1970s and the US in 2014. The future of testosterone deficiency treatment may include novel therapies such

as androgen receptor modulators and other methods to increase endogenous testosterone production.

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N3.2

Abstract unavailable

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Endocrine nurse achievement session

N4.1

Abstract unavailable

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N4.2

Education programmes for patients with adrenal insufficiency: Evaluations based on patients experiences

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Introduction
Adequate hormone replacement therapy in adrenal insufficiency (AI) is essential. Patients should have basic knowledge about their condition and how to minimise the change on an adrenal crisis. Education on how and when hydrocortisone replacement therapy should be adjusted together with instruction and practice an emergency injection are considered important measures to prevent a crisis. A nurse-led group-based education programme (GEP) was developed, and given from September 2018 until March 2020. In an aim to provide patients with education during COVID-19 pandemic, a video was developed based on the GEP. Both ways of education are evaluated.
Methods
Patients who followed the GEP ($n=67$) or watched the video ($n=139$) were recruited to fill in a questionnaire in retrospect. The questionnaire assessed experiences on content, contact with clinical nurse specialist and applicability in daily life. Furthermore, it contained self-reported marks before and after education, multiple choice and open questions. Also, electronic medical records for demographic data were studied.
Results
The composition of both groups seems similar when looking at gender and age. In the GEP-group 48,8% was men versus 54,7% in the video-group. The average age of the GEP-participants was 57.6 years compared with 58.0 years in the video-group. Remarkable is a doubling of the percentage participants with AI as a result of immunotherapy in the video-group. The self-reported marks were significantly improved after the GEP (P0.003). In the video-group, first analysis also showed an increase in the mean of self-reported marks from 4.81 (SD 2.6) to 7.3 (SD 1.4). In both groups the desire for repetition was regularly mentioned. Especially the video-group participants indicated they would like to receive the education sooner after diagnosis and guided practising the emergency injection was missed.
Conclusion
Overall, repeated education was explicitly indicated by a large proportion of participants in both groups. Further analysis in the video-group is being conducted.

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Professional development session and awarding

N5.1

Careers for Nurses Beyond Bedside: 1. Careers in Academia; 2. Careers in Pharmaceutical Industries

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Unlike many other academic disciplines nursing is a relative newcomer to higher education in many countries. Although baccalaureate level preparation has been available in various forms since 1920 the real momentum for graduate nursing at point of qualification accelerated in the 1980s and 1990s. The development of nurse graduate education has nevertheless brought the realisation of many long fought professional ambitions but also created an academic nursing workforce. This can feel to newly appointed academic staff more akin to a second career undertaken in a parallel universe; and a journey sometimes embarked upon ill-prepared. This presentation will seek to describe the modern University and differences between research intensive and teaching orientated institutions. This will serve as a backcloth to explain the challenges for new nursing academics delivering education to meet regulatory, professional and workforce requirements whilst carving their own research and scholarly aspirations. This will be contrasted with the development of clinical academic roles namely PhD prepared clinical leaders combine clinical leadership with active engagement in research and may hold joint or honorary positions in higher education institutions. Lastly strategies that can be employed to navigate a successful career in academia to better contribute to the future of nursing and future generations of nurses will be discussed.

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Oral Communications

Oral Communications 1: Diabetes, Obesity, Metabolism and Nutrition 1

OC1.1

Fish oil supplementation during pregnancy attenuates sex-specific changes induced by perinatal maternal high-fat diet in mitochondria of rat skeletal muscle at weaning

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Perinatal maternal high-fat (HF) and isocaloric diet induced obesity and metabolic disorders in the offspring since weaning. At adulthood, oxidative soleus skeletal muscle of HF male offspring exhibited lipid accumulation and mitochondrial damage. At birth, HF offspring have higher n-6:n-3 polyunsaturated fatty acids (PUFA) plasma ratio. We hypothesized that HF offsprings mitochondria of skeletal muscle exhibit damages at weaning that could be mitigated by fish oil (FO, rich in n-3PUFA) supplementation during pregnancy. Female Wistar rats consumed an isocaloric, control (C: 11% lipids) or high-fat diet (HF: 29% lipids) from 8 weeks preconception until lactation. Part of the HF mothers received HF diet supplemented with FO (3%, HFFO: 35% lipids) only during pregnancy. FO did not attenuate the increase in weight gain, glycemia, and adiposity induced by maternal HF diet in male (M) and female (F) offspring at weaning. In the soleus muscle, HF-M offspring tended to higher content of triglycerides ($P=0.08$). HF-F offspring tended to a higher content of monounsaturated fatty acids ($P=0.06$) and a higher rate of de novo lipogenesis ($P=0.01$). FO increased the docosahexaenoic acid content in soleus of both sexes ($P<0.05$). HF-M and -F offspring showed reduced mitochondria density. They exhibited misalignment of sarcomeres, increased damaged mitochondria ($P<0.0001$), with reduced mitochondrial area ($P<0.0001$) and perimeter ($P<0.0001$), attenuated by FO ($P<0.05$). HF-M exhibited lower protein expression of mitochondrial biogenesis marker PGC1α ($P=0.04$), mitochondrial transcriptional factor *Tfam* mRNA ($P=0.06$), thermogenic/mitochondriogenesis marker *Sln* ($P=0.002$), uncoupling protein 3 (UCP3: $P=0.059$), and antioxidant protein mitochondrial superoxide dismutase ($P=0.03$) suggesting impaired mitochondriogenesis and increased oxidative stress, mechanisms contributing to reduced mitochondria density and to higher damaged mitochondria. Decreased mitochondrial fission marker (p-DRP1, $P=0.02$), concomitant with smaller and less circular mitochondria, suggests reduced fission. FO attenuated these changes and, additionally, increased the fusion marker mitofusin-2. Electron transport chain proteins were unaltered in HF offspring of both sexes, however, HFFO-M exhibited increased mitochondrial complexes I ($P=0.005$) and III ($P=0.04$). Differently, HF-F exhibited lower protein expression of mitochondrial fusion marker OPA1 ($P=0.02$ vs C), reversed by FO ($P=0.03$) accompanied by larger mitochondria, suggesting increased fusion that may contribute to reduced mitochondrial density in HFFO-F ($P=0,0002$ vs HF). Additionally, FO increased PGC1α ($P=0.03$) and UCP3 ($P=0.06$), partially attenuating mitochondria damage. Therefore, maternal FO supplementation during pregnancy partially mitigates sex-specific alterations in skeletal muscle mitochondria induced by maternal HF diet in offspring at weaning, which may have repercussions on offspring phenotype throughout life.

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OC1.2

Semaglutide alters tongue transcriptome along with the improvement of taste perception and increased brain activation in response to sweet tasting solution in obese women with PCOS

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Background
Obese individuals may perceive the taste of caloric dense food as less intense, resulting in decreased activation of the reward system. Preclinical research provides some insights into the role of GLP-1 in the gustatory coding. The impact of GLP-1 receptor agonists on the tongue and taste perception remains largely unaddressed in clinical settings.
Aim
to investigate the impact of semaglutide on the tongue transcriptome, taste perception and brain response to visual food cues and sweet tasting solution.
Methods
Thirty obese women with polycystic ovary syndrome (age 33.7 $\pm$ 6.1 years, BMI 36.4 $\pm$ 4.4 kg/m^2, mean $\pm$ SD) were randomized to once weekly semaglutide (SEMA) 1.0 mg s.c. or placebo in a 16-week, single-blind, placebo-controlled study. Participants underwent the biopsies of the tongue. Transcriptomic profile of tongue tissue was assessed as changes in expression level measured by RNA sequencing (NovaSEQ 6000 sequencer, Illumina). Taste sensitivity was evaluated by chemical gustometry using a validated examination method consisting of 16 taste strips including 4 different concentrations of sweet, sour, salty and bitter. The change in neural response to visual food cues and to sweet-tasting solution was assessed by functional MRI. In the first task, subjects were shown a series of calorie-dense, calorie-low food and non-food cues. In the second task, the neural responses to the tasting of sweet solution dripped on the tongue was assessed. Both tasks were performed in fasting state and repeated after the meal ingestion. Change in eating behaviour was evaluated by the Three-Factor Eating Questionnaire (TFEQ-R18).
Results
A total of 1326 genes were differentially expressed in the tongue tissue between the SEMA and placebo with log FC >0.7 or $<.7$ and FDR <0.05. Gene ontology analysis identified altered pathways in WNT signalling, fat cell differentiation, reproductive regulation and carbohydrate and fatty acid metabolism. Semaglutide improved taste sensitivity for all four basic tastes. The ability to resist emotional eating improved in SEMA group. Furthermore, semaglutide decreased activation in response to food pictures in the right putamen after the meal ($P<0.001$) and increased activation in response to sweet solution in the region of angular gyrus ($P<0.001$).
Conclusion
Semaglutide modified transcriptomic profile in the tongue along with improved taste perception. Furthermore, it decreased activation in putamen in response to high caloric food cues and increased activation of angular gyrus in response to sweet tasting solution. This implies an impact of semaglutide on gustatory coding up to brain integrative centres.

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OC1.3

Neuronostatin receptor GPR107 as a potential biomarker and therapeutic target in chronic liver disease

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Metabolic associated fatty liver disease (MAFLD) is rapidly becoming a major aetiology for the development of hepatocellular carcinoma (HCC, the most common liver cancer) in the context of chronic liver disease. Current therapeutical options for MAFLD (dietetic/lifestyle intervention and/or pharmacological approaches) are still insufficient and the cellular and molecular mechanisms underlying this disease are yet to be fully understood. Our group previously reported that the neuronostatin (NST)/GPR107 system could be used as a potential biomarker in prostate cancer progression and aggressiveness. Therefore, we aimed to explore the role of NST and its putative receptor GPR107 in the MAFLD-HCC spectrum. For this purpose, GPR107 expression was analysed in 2 internal retrospective cohorts with chronic liver disease samples [cohort 1: HCC vs adjacent tissue ($n=93$)/cohort 2: HCC vs adjacent ($n=58$), cirrhotic ($n=39$) and healthy tissue ($n=5$)], 13 external validation cohorts (6 with HCC and 7 with MAFLD) and 3 liver cancer cell lines (HepG2, Hep3B and SNU-387). Functional assays (proliferation, wound healing, colony and hepatosphere formation) were also implemented in liver cancer cells to evaluate the impact of NST application and/or GPR107 expression modulation (overexpression/silencing). Overexpression of GPR107 in tumour samples was observed in cohort 1 and validated in 5 out of 6 external HCC cohorts. Moreover, GPR107 expression levels positively correlated with key cancer aggressiveness

biomarkers (e.g. MKI67, CDK1, RB, C-MYC), and were associated with microvascular invasion. In 4 out of 7 external MAFLD cohorts, we detected a gradual increase in GPR107 expression through the MAFLD-HCC progression, suggesting a role in hepatocarcinogenesis. Regarding GPR107 expression in cell lines, it was primarily detected in Hep3B, followed by SNU-387, and was not detected in HepG2. Functional assays revealed a decrease in cell proliferation in response to NST in all studied cell lines. On the other hand, GPR107 overexpression in Hep3B and SNU-387 increased, while its silencing decreased, cell proliferation. Lastly, combined NST administration and GPR107 overexpression reduced Hep3B and SNU-387 proliferation vs GPR107 overexpression alone, whereas the combination of NST application and GPR107 silencing showed no significant difference from GPR107 silencing. Altogether, our data demonstrate that GPR107 is overexpressed in the MAFLD progression towards HCC, suggesting that the NST/GPR107 system might be a novel vulnerability in chronic liver disease, and that could be exploited as a diagnostic and prognostic biomarker and a therapeutic target in MAFLD-HCC.

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OC1.4

Associations between handgrip strength and skeletal muscle mass with all-cause mortality and cardiovascular mortality: a prospective cohort study of UK Biobank

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Background
Handgrip strength (HGS) and skeletal muscle mass (SMM) are associated with all-cause and cardiovascular disease (CVD)-specific mortality risk in type 2 diabetes (T2DM) patients. However, the pattern of this association was unclear. We aimed to explore the pattern of associations between HGS and SMM with all-cause and CVD mortality risk in a diabetic population.
Method
Data were obtained from the UK Biobank (application number 92014), a large prospective cohort study. HGS was measured using a Jamar J00105 hydraulic hand dynamometer, and the mean values of left and right HGS were expressed in absolute units (kg). SMM was measured using bioelectrical impedance method. Considering the influence of individual body size, SMM/height^2 was used for subsequent analysis. Death data are available via links to the National Health Service Information Centre.
Results
The mean age of the 13392 T2DM patients was 60.39 $\pm$ 6.76 years and 8350 (52.35) were male. With a mean follow-up of 12.52 years, there were 3006 (22.45%) deaths, including 746 (5.57%) CVD deaths. Cox proportional risk model showed that compared with the highest quartile of HGS (Q4), the all-cause and CVD mortality risk increased progressively with decreasing muscle strength (P-trend <0.05). As a continuous variable, a 1 SD decrease in HGS was found to increase the risk of all-cause mortality by 30.9% in men (HR: 1.309, 95% CI: 1.241-1.381) and 25.6% in women (HR: 1.256, 95% CI: 1.112-1.420); the risk of CVD mortality increased by 35.0% in men (HR: 1.350, 95% CI: 1.219-1.496) and 43.4% in women (HR: 1.434, 95% CI: 1.087-1.894). Decreased SMM/height^2 was not associated with increased mortality risk when SMM/height^2 was quartile divided and when used as a continuous variable. However, when the third quartile (Q3) of SMM/height^2 was used as a reference, an increased mortality risk was found in men for Q1 and in women for both Q1 and Q4 . The multivariable restricted cubic regression splines with 4 knots showed that there was no non-linear evidence between HGS with all-cause mortality and CVD mortality risk (Pnon-linear >0.05), while SMM/height^2 showed a U-shaped non-linear relationship with all-cause mortality and CVD mortality risk (Pnon-linear <0.05).
Conclusion
HGS showed a linear downward trend with mortality risk, whereas SMM/height^2 showed a U-shaped relationship, and either too low or too high muscle mass was associated with increased risk of CVD and all-cause mortality. Because HGS is a simple, non-invasive, and inexpensive measure, it could be used to predict mortality risk.

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Oral Communications 2: Thyroid

OC2.1

Randomized double-blind placebo-controlled trial on levothyroxine and liothyronine combination therapy: The levolio study

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Introduction
Despite normal thyroid-stimulating hormone serum levels, up to 60% of hypothyroid patients are dissatisfied with the treatment. Animal studies suggest that the persistence of symptoms may derive from peripheral hypothyroidism. Combination treatment with levothyroxine and liothyronine is a theoretically plausible solution but its efficacy is still questionable.
Aim
To evaluate the effects of personalized twice-daily combination therapy on peripheral tissues and quality of life in thyroidectomized patients, considering also the influence of genetic variants of *DIO2* and *MCT10*.
Methods
Double-blind, randomized, placebo-controlled study in which 141 thyroidectomized subjects, with serum thyroglobulin <0.2 ng/ml and negative anti-thyroglobulin antibodies, with TSH within the normal range, were randomized to study (levothyroxine + liothyronine in the morning and liothyronine in the evening; $n=70$) or placebo group (levothyroxine + placebo in the morning and placebo in the evening; $n=71$). Pituitary-thyroid axis compensation was assessed after 6, 12 and 24 weeks. Clinical parameters, quality of life (evaluated with ThyPro-39 questionnaire), tissue markers (sex hormone binding globulin, serum lipids, bone metabolism markers) were evaluated at 12 and 24 weeks. *DIO2* and *MCT10* single nucleotide polymorphisms were genotyped.
Results
At baseline, both groups had free triiodothyronine/thyroxine (fT3/fT4) ratio below the physiologic range, which normalized after 6 months only in the study group (0.32 $\pm$ 0.08 vs 0.26 $\pm$ 0.05, $P<0.001$). Combination treatment required greater dose adjustments (25% vs 54%, $P<0.001$), due to TSH reduction below the reference range, with no signs or symptoms of hyperthyroidism. After 6 months, the study group had improved emotionality, anxiety, depression, and overall impact of the disease on quality of life ($P<0.05$). However, no preference for combination therapy was recorded. Tissue markers of peripheral thyroid function and BMI did not change in either group. Genetic variants did not influence any of the analyzed outcomes.conclusions: Six months of combination treatment normalizes fT3/fT4 ratio, improves quality of life but does not lead to changes in known tissue markers. However, therapeutic schemes and liothyronine formulation still need to be improved.

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OC2.2

Faecal microbiota signature in hypothyroid patients with refractoriness to levothyroxine treatment

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Despite an accurate management, in about 20% of hypothyroid patients showing an increased need for oral levothyroxine (LT4), the leading cause of treatment refractoriness remains unknown. Some studies hypothesized the relationship between gut microbiota composition and thyroid homeostasis, but the possible involvement of microflora in the efficacy of LT4 treatment has not been evaluated yet, and this represents the aim of our study. We examined the faecal microflora composition of 48 euthyroid (TSH <0.8-$2.5>$ mU/l) patients with Hashimoto's thyroiditis, subdivided in three groups: A) 13 patients not treated with LT4 (median age = 52 years); B) 22 patients reaching target TSH with a dose of LT4 of 1.24 mg/ kg/day (median age = 49 years); C) 13 patients reaching target TSH with a high dose of LT4 of 1.75 mg/kg weight/day (+35%; $P=0.0001$) (median age =

56 years). All treated patients took LT4 in fasting state, avoiding food and drugs interfering with LT4 absorption and action. Moreover, none of the included patients followed unbalanced diets, had disorders or used drugs interfering with faecal microbial composition. From each patient fecal samples were provided. Microbiota composition was determined via 16s rDNA sequencing of the hypervariable region V3-4 on Illumina MiSeq. Alpha and beta-diversity indices and all statistical analysis were computed in Qiime2. The gut microbiota of groups A and B showed a similar composition, while patients with refractoriness to L-T4 treatment (group C) showed a lower relative abundance of Firmicutes (66.58%) as compared to those in group A (76.8%, $P = 0.039$) or in group B (80.8%,$P = 0.012$). By contrast, patients of group C showed significantly increased Bacteroidetes (21.5%) as compared to both groups A and B ($P = 0.04$), as well as significantly higher relative abundance of Proteobacteria (9.28 vs 2.89% $P = 0.04$) as compared to patients with normal L-T4 absorption. By merging group A and B together, it appears that the ratio between Firmicutes and Bacteroidetes is more than doubled in patients with T4 refractoriness (3.05 to 6.28). Alpha-Diversity Analysis revealed that patients of group A who showed higher Shannon's Diversity as well as Pielou's evenness indexes as compared to patients of group C. Beta-Diversity Analysis measured as weighted UniFrac showed a statistically significant clustering (A vs C;$P = 0.006$ and B vs C;$P = 0.018$). This is the first analysis of fecal microbiota composition in patients with refractoriness to levothyroxine treatment, showing that a peculiar microbial signature characterizes patients with high levothyroxine requirement.

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OC2.3

The variable clinical spectrum of Thyroid Hormone Resistance Syndrome type β: two different presentations of the same disease

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Thyroid hormone resistance syndrome(THRS) occurs in 1:40000 live births and can be diagnosed after a period of enigmatic changes in thyroid hormones(TH). Patients may be clinically euthyroid, have clinical hypo or hyperthyroidism. Mostly,it is an autosomal dominant disease due to germline mutations in THRβ-gene(exons 7-10). Resistance to peripheral action of TH leads to absence of TSH suppression (which can be normal/elevated) despite elevated fT4 and fT3.

Case 1:

A 38-year-old-man was referred because of persistent elevations of TH (TSH 43 µUI/ml (0.4-4.0), fT4 2.7 ng/dl (0.7-1.5), fT3 3.4 pg/ml (1.8-4.2)) – together with depression, a palpabre goitre and hyperlipidemia; his sister had "hypothyroidism". The pituitary-MRI excluded a thyrotropinoma; the remaining pituitary function was normal. Autoimmune thyroid disease was excluded. Genetic analysis confirmed a heterozygous G344R mutation(exon 9) in THRβ-gene: his sister had the same mutation; his 11-year-old daughter had normal TH. He begun treatment with levotyroxine(L-T4) up to 200 µg/daily: TSH reduced to 27 µUI/ml, fT4 1,8 ng/dl, fT3 4,1 pg/ml. The patient improved substantially, but lost follow-up until 15 years later, when he presented with TSH 112 µUI/ml, fT4 1,9 ng/dl, fT3 4,1 pg/ml under L-T4 125 µg/daily. He had gained weight, attempted suicide,and had elevation of CK and liver enzymes. He resumed the 200 µg/daily L-T4 dose: TSH decreased to 73 µUI/ml and he clinical and biochemical improved.

Case 2:

A 20-year-old-woman with short stature(148 cm), sensorineural deafness and attention deficit disorder, with TSH 5,4 µUI/ml, fT4 4,1 ng/dl, fT3 4,3 pg/ml was diagnosed with THRS after a confirmed heterozygous G344R mutation in THRβ-gene. Her brother had the same mutation. She underwent hemithyroidectomy due to a follicular adenoma and TSH slightly increased to 6,9 µUI/ml. She was under liothyronine, with maximum doses of 25 µg/bid: TSH 5,0 µUI/ml, fT4 1,8 ng/d, fT3 4,2 pg/ml. At 47-years-old, she is not under any thyroid replacement hormone but begun atenolol due to palpitations and insomnia: TSH 4,2 µUI/ml, fT4 2,29 ng/dl and fT3 7,0 pg/ml (1,8-4,2).

Discussion

Frequently, THRS treatment is not necessary unless signs of decompensation appear (great elevation of TSH together with elevated fT3 and fT4 levels), common if concomitant thyroiditis or previous ablative therapy. The woman from case 2 underwent thyroid surgery, however TSH remained minimally elevated, and years later she developed hyperthyroidism. In case 1, despite the absence of apparent causes for the decompensation, high doses of L-T4 were needed to resolve clinical hypothyroidism. More case reports are needed to better understand the course of this widely variable clinical presentation disease.

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OC2.4

TSH suppression increases the risk of sarcopenia and frailty in the long-term follow-up of elderly patients with differentiated thyroid carcinoma

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Objective

In differentiated thyroid carcinoma (DTC), TSH suppression with levothyroxine (L-T4) is a standard treatment for reducing tumor recurrence after total thyroidectomy. This study aims to evaluate the effect of long-term TSH suppression on the development of sarcopenia and frailty in elderly patients with DTC.

Method

Seventy patients aged 60 years and older with stable TSH levels during the last year and under L-T4 due to DTC were included in the study. The anterior thigh muscle thickness was measured by ultrasound and the Sonographic Thigh Adjustment Ratio (STAR) Index was calculated. Reduced muscle strength was diagnosed with a hand grip test. Walking speed, Fried Frailty Index and the Physical Activity Scale for the Elderly (PASE) scores were calculated.

Results

Median age of the patients was 65 years (min-max: 60-80) and 64.3% were women. The patients were followed up for 11 (2-30) years. Median TSH was 1.10 µIU/ml (IQR = 1.13). While active suppression (TSH < 0.1) was applied to 4.3% of the cases, 22.9% had low (0.1-0.49), 60.0% had low-normal (0.5-2), and 12.9% had normal (2.1-4) TSH levels. The anterior thigh muscle thickness was 37.5 (9.5) mm, and the STAR Index was 1.21 (0.39). Muscle mass was reduced in 35.7% of the cases. TSH was found to be significantly low in the group with reduced muscle mass compared to the group having no muscle mass reduction (0.71 (1.07) vs 1.20 (1.08); $P = 0.014$). Reduced muscle strength was present in 17.2% of the patients in the hand grip test. TSH levels of the reduced muscle strength group was lower than normal muscle strength group (0.66 (0.97) vs 1.18 (1.17); $P = 0.037$). According to the Fried Frailty Index, 58.5% of the cases was prefrail and/or frail while the remaining cases were robust. TSH was lower in the group at high risk of frailty than in the robust group (0.77 (0.88) vs 1.39 (1.07); $P = 0.002$). TSH showed a positive correlation with walking speed ($r = 0.258$, $P = 0.031$) and STAR Index ($r = 0.254$, $P = 0.034$), and a negative correlation with Fried Frailty Index ($r = -0.399$, $P = 0.001$). TSH below 1.325 µIU/ml was found to increase the risk of frailty with a sensitivity of 80.49% and a specificity of 58.62% (AUC = 0.719, $P = 0.001$). Logistic regression analysis indicated that TSH was an independent predictor of frailty development ($P = 0.006$).

Conclusion

In elderly patients with TSH suppression due to DTC, muscle strength and muscle mass decrease, and the risk of frailty increases in the long term. Close follow-up of these patients for sarcopenia and frailty is recommended.

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OC2.5

Circulating Long Non-Coding RNAs as a non-invasive markers to help differentiate benign from malignancy in indeterminate thyroid nodules

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Introduction

Molecular testing is being increasingly used to detect malignancy in indeterminate thyroid nodules (Bethesda 3 & 4) which pose diagnostic dilemma. Long non-coding RNAs are crucial for metastasis, angiogenesis, and tumour growth of various cancers. Clinical utility of plasma lncRNAs as non-invasive diagnostic markers for thyroid cancer especially in indeterminate nodule remains unexplored.Methodology: We selected lncRNAs relevant to thyroid neoplasm from LncRNA Disease 2.0 database. The lncRNAs thus selected were PVT1, HOTAIR, NEAT1, MALAT1, BANCR, HOTTIP, GAS5, H19, and GAS8-AS1. We compared the expression (using quantitative real-time PCR (qRT-PCR)) of these lncRNAs in biopsy proven differentiated thyroid cancer patients versus benign thyroid nodule subjects and healthy controls as part of first phase of study (discovery cohort). We then proceeded to determine cut-off of change of level of expression (ΔCT) for these lncRNAs (by performing a Receiver operating-characteristic (ROC) curve. These cut-offs was then applied in a validation cohort

to test the ability of the same to help differentiate benign from differentiated thyroid malignancy (indeterminate nodules). We also determined the expression of these lncRNAs in FNAC materials and tissue samples for cross validation. Finally we rechecked the expression in plasma 2 weeks after surgery.
Results
We compared the plasma expression of the nine circulating lncRNAs in patients with thyroid cancer ($n=25$), benign thyroid nodules ($n=40$), and healthy controls ($n=39$) in the discovery cohort and the expression of PVT1, MALAT1, and BANCR were found to be significantly different between benign and malignant nodules ($P<0.001$). Cut off for ΔCT (obtained by ROC) for PVT1, MALAT1 and BANCR were 4.64, 6.28 and 5.94 respectively. We applied these cut-offs in a validation cohort (N=158, indeterminate nodules) and PVT1, MALAT1 and BANCR was able to differentiate malignant from benign nodule with 96.20%, 87.34% and 84.81% accuracy. PVT1 and BANCR were up-regulated in all differentiated thyroid cancer but MALAT1 was only up-regulated in PTC, but not in FV-PTC and FTC. Cross-validation of our data in FNAC material and histopathology sample reconfirmed our findings (PVT1, MALAT1 and BANCR were up-regulated similar to that in plasma (similar quantum of increased expression)). Post-operatively plasma samples were tested and it was found that the over expression of PVT1, MALAT1 and BANCR normalized to levels similar to benign nodules.
Conclusion
Plasma PVT1, MALAT1, and BANCR may be useful molecular non-invasive diagnostic markers to help differentiate benign from malignant thyroid nodules, including in those presenting with indeterminate thyroid nodules.

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OC2.6

CD3+CD8+CD20+T lymphocytes behave differently in autoimmune thyroiditis and related polyautoimmune disorders: A pilot study

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The presence and the role of $CD20^+$ T cells in humans has been described in autoimmune disorders such as multiple sclerosis and rheumatoid arthritis. In healthy subjects, $CD3^+CD20^+$ T cells are detected in all lymphatic organs and in the cerebrospinal fluid and represent about 5% of circulating T cells. Some reports described their production of high levels of IL-17A and/or IFN-γ. This study was aimed at investigating the behavior of $CD3^+CD20^+$ T lymphocytes in patients with Hashimoto's thyroiditis, isolated or in a frame of polyautoimmunity. Sixty five patients with HT, aged from 23 to 69 years (M=14; F=51), 23 of whom in isolated form and 42 with a further autoimmune disorder [16 with gastric atrophy (HT+GA), 15 with vitiligo (HT+V) and 11 with celiac disease (HT+CD)] were investigated. Twenty sex- and age-matched healthy subjects represented the control group (HD). The chronic use of interfering drugs, the presence of severe or chronic disorders, pregnancy and lactation were considered as exclusion criteria. Whole blood samples were obtained and quickly stained with the specific fluorescent-labelled antibodies. Red blood cells were then lysed by adding 1 ml of hypotonic buffer and samples were analyzed on a FACs ARIA II Flow Cytometer (BD). The percentages of $CD3^+CD20^+$ T and the one of $CD4^+CD20^+$ T lymphocytes were similar in all groups. The subpopulation $CD8^+CD20^+$ T in the whole group of autoimmune patients was higher than in HD ($P=0.0089$). Those with isolated HT also showed higher percentages of $CD8^+CD20^+$ T than in HD patients, without reaching statistical significance. $CD8^+CD20^+$ T cells subset was clearly different (ANOVA:$P=0.0058$) in the presence of associated autoimmune disorders, as compared with HD. In particular, an increased percentage of these cells was observed in HT+GA as compared to HD ($P=0.0257$), unlike in patients with HT+CD, all in gluten-free diet, in whom the $CD8^+CD20^+$ T cells subset was similar to the one in HD. Interestingly, when subdivided by thyroid function, HT hypothyroid patients showed a doubled percentages of $CD8^+CD20^+$ T cells than in euthyroid patients and in HD ($P=0.0115$). These preliminary findings indicate that the presence of $CD8^+CD20^+$ T lymphocytes is associated with a worst thyroid function and it is differently modulated in HT patients with or without poly-autoimmunity.

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Oral Communications 3: Pituitary and Neuroendocrinology 1

OC3.1

Diagnosing Vasopressin Deficiency (Central Diabetes Insipidus) using Copeptin following Hypertonic Saline and Arginine Stimulation

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Background
The main challenge in the diagnosis of arginine vasopressin deficiency (AVP-deficiency, formerly known as central diabetes insipidus), is its distinction against primary polydipsia. Hypertonic saline stimulated copeptin showed a high diagnostic accuracy of 97% in distinguishing between AVP-deficiency and primary polydipsia (Fenske W, Refardt J, NEJM 2018), but comprises discomfort for patients and requires close sodium monitoring. Arginine stimulated copeptin showed a similar diagnostic accuracy of 93% (Winzeler B, Lancet 2019) with the test being generally well tolerated. A head-to-head comparison is needed to find the best diagnostic test. We hypothesize that the arginine stimulation test is non-inferior to the hypertonic saline stimulation test (non-inferiority margin 10%) for the diagnosis of AVP-deficiency with an easier test protocol and better tolerability.
Methods
Between 2018 and 2022, 164 patients with hypotonic polyuria from seven tertiary medical centers underwent hypertonic saline and arginine stimulation in randomized order for diagnostic evaluation. Serum copeptin levels were measured at sodium-level of >149 mmol/l after hypertonic saline and 60 minutes after arginine infusion, respectively. The final diagnosis was made after treatment response at three-month follow-up blinded to copeptin levels. The main outcome measure was the overall diagnostic accuracy using the pre-defined copeptin cut-off of 4.9 pmol/l for the hypertonic saline and 3.8 pmol/l for the arginine stimulation.
Results
Of the 157 evaluable patients, 69 (44%) were diagnosed with AVP-deficiency and 88 (56%) with primary polydipsia. Of the 69 AVP-deficiency patients, 41 (59%) were judged to have a complete and 28 (41%) to have a partial defect. Copeptin samples are currently being measured in batch analysis and the diagnostic accuracy and tolerability results of both tests will be presented at the Endocrine Society meeting.
Conclusion
This prospective multicentre study will determine which test should be used for the differentiation between AVP-deficiency and primary polydipsia.

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OC3.2

Protein supplementation increases plasma sodium levels and urinary urea excretion in patients with chronic SIAD – A monocentric open-label proof-of-concept study -The treasure study

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Introduction
The syndrome of inappropriate antidiuresis (SIAD) is the most common cause of euvolemic hyponatremia. Besides fluid restriction, increasing free water clearance is an effective treatment approach that can be achieved through osmotic diuresis by administering oral urea. Dietary proteins are metabolized into soluble excretable urea by the liver. We hypothesized that dietary protein could increase free water clearance through urea-induced osmotic diuresis and therefore aimed to investigate the effect of high-protein supplementation on plasma sodium levels in outpatients with chronic SIAD.

Methods
This is an interim analysis of a monocentric open-label proof-of-concept trial conducted at the University Hospital of Basel in Switzerland since October 2021. Adult outpatients with chronic SIAD of any etiology were eligible. Patients received 90 g protein daily for 7 days in the form of protein powder dissolved in a maximum of 1L of liquid of choice. After a wash-out period of at least a week, patients received 30 g of oral urea daily for 7 days. Patients were asked to keep their baseline fluid intake unchanged throughout the study. The primary endpoint was the increase in sodium levels from baseline to the end of the 7-day protein supplementation.
Results
Fourteen patients, 11 females and 3 males, with chronic SIAD were included. Median [IQR] age was 68 [61, 80] and median duration of hyponatremia was 21 months [3, 59]. At baseline, median plasma sodium concentration was 130 mmol/l [128, 133]. Eight patients had mild hyponatremia (130-134 mmol/l), 4 had moderate hyponatremia (125-129 mmol/l), and 2 patients had profound hyponatremia ($<$125 mmol/l). After 7 days of 90 g daily protein supplementation ($n=14$), sodium levels increased by a median of 3.5 mmol/l [0.5, 5.8], blood urea nitrogen increased by a median of 4.3 mmol/l [1.7, 5.1] and urinary urea corrected for urine creatinine increased by a median of 25.3 mmol/mmol [15.6, 31.2]. After 7 days of oral urea ($n=8$), sodium levels increased by a median of 2 mmol/l [1, 3], blood urea nitrogen increased by a median of 8.5 mmol/l [3.8, 10.2] and urinary urea corrected for urine creatinine increased by a median of 31 mmol/mmol [21.1, 39.8].
Conclusion
This analysis suggests that high-protein supplementation with protein powder increases plasma sodium levels in patients with chronic SIAD. The increase in urea concentration in both plasma and urine upon protein supplementation is comparable to the increase upon oral urea administration, which supports protein-induced ureagenesis to be the underlying mechanism of action.

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OC3.3

[18F]FET PET-MRI; a novel and improved technique for detection of small functional pituitaryadenomas

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Background
Small functional pituitary adenomas can cause severely disabling symptoms and early death, however, surgical planning is often complicated due to inconclusive diagnostic MRI in up to 40% of patients and therefore hamper cure rates. We here introduce a novel method for the detection of small functional pituitary adenoma by O-(2-[18F]-fluoroethyl)-L-tyrosine ([18F]FET) PET-MRI.
Methods
Patients with Cushing's disease (CD) or acromegaly with a suspected primary or recurrent small functional pituitary adenoma underwent [18F]FET PET-MRI. Focal uptake of [18F]FET was evaluated by a single nuclear radiologist and MRI was separately evaluated by a single neuroradiologist. Outcomes were compared with clinical follow-up and sensitivity and positive predictive values (PPV) were calculated.
Findings
Consecutive 28 patients, 68% female, mean age 50 years (range: 24 – 71), with CD ($n=22$; 79% or acromegaly ($n=6$; 21%) were scanned. 17 CD patients with a primary diagnosis had also undergone IPSS and 3 (50%) had a primary acromegaly diagnosis. 14/22 CD patients (64%) and 1/6 acromegaly underwent transsphenoidal surgery after [18F]FET PET, others are waiting or refused. Twenty-two CD patients (100%) had a positive [18F]FET PET, allowing to identify pituitary adenomas as small as 3 mm in size on accompanying MRI. 11/14 CD patients who underwent subsequent transsphenoidal surgery are biochemically in remission; rendering an estimated sensitivity of 100% and a PPV between 78 – 100% to detect CD. Four acromegaly patients (67%) had a positive [18F]FET PET. One acromegaly patient was biochemically in remission after transsphenoidal surgery.
Conculsion
[18F]FET PET-MRI shows high accuracy for localizing small functional pituitary adenoma in patients with CD and acromegaly. The diagnostic yield of this hybrid imaging technique exceeds that of MRI alone and IPSS and provides a welcome improvement for diagnosis, planning of surgery and follow-up.

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OC3.4

Measurements of growth hormone using dried blood spots in preterm neonates: reference values and longitudinal evaluation.

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Background and Aim
Congenital growth hormone deficiency (cGHD) is a rare but life-threatening condition whose diagnosis is challenging in the absence of reliable reference values, both in healthy neonates and in preterm ones. We recently estimated GH reference interval in 1036 healthy, at-term newborns (HN) form dried blood spot samples using a previously validated analytical method. Aim of this study is to provide values for random GH in preterm newborns (PN).
Methods
GH was evaluated in 78 PN (M:F 51:49%) attending the Neonatal Intensive Care Unit of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan. GH measurement was performed as above described at 48 hours after birth (GH1). In 41 out of 78 PN a second GH determination (GH2, at 15 days after birth) was also available.
Results
Median (IQR) GH1 values were 14.9 µg/l (9.8-21.1). No gender differences were found ($P=0.089$). The percentile 5th (3.4 µg/l) calculated in PN was lower than the lower limit of reference interval estimated in HN (reference limit at percentile 5.0th: 7.0 µg/l, 90%CI 6.7-7.3). In PN, decreasing GH levels were associated with increasing invasiveness of ventilation (no ventilation: 20.1, CPAP/biphasic: 15.1, high flows ventilation: 12.4, invasive ventilation: 5.4; overall KW $P=0.026$). Indeed, GH was significantly lower in PN needing invasive ventilation than not ventilated ones (Bonferoni's correction $P=0.048$). A low-to-moderate, although significant, correlation (rho$=0.295$, $P=0.009$), was found between GH levels and gestational age (GA). No association was, instead, found with maternal age ($P=0.072$), smoke ($P=0.138$), parity ($P=0.520$) or other neonatal variables, including jaundice ($P=0.276$) and auxological parameters (all $p>0.05$). Considering PN with both GH determinations ($n=41$), GH1 levels were significantly higher than GH2 (14.4 vs 9.8 µg/l, respectively, $P=0.018$). GH decreased in most neonates (26/41$=$63%), as expected after the first week of life. Interestingly, in PN with GH increase (GH2$>$GH1), GA was significantly lower than in those with GH decrease (GH1$>$GH2), with a median 30 vs 33 weeks ($P=0.024$).
Conclusions
Our data show for the first time that PN have lower median GH levels than HN. GH in PN is associated with ventilation and GA. The latter finding, along with the association between lower GA and increase in GH2 levels could be explained by an incomplete maturity at birth of the somatotropic axis in very PN, with the subsequent GH increase reflecting an extra-uterine maturation of the axis itself.

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OC3.5

Interest of serum and salivary cortisol diurnal cycle in the positive diagnostic of Cushing syndrome and in the differential diagnosis of pseudo-Cushing syndrome

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Introduction
Biological diagnosis of Cushing syndrome relies on three parameters: 24 hours-free urinary cortisol; serum cortisol after 1 mg dexamethasone suppression test; late-night serum or salivary cortisol. These tests allow the diagnosis of cortisol

excess but do not help in etiological diagnosis, particularly in the distinction between pseudo-Cushing and ACTH-dependent Cushing syndrome, which is often challenging. The aim of this study was to evaluate the performances of cortisol diurnal cycle in serum and saliva for both the positive diagnosis of Cushing syndrome and the differential diagnosis of pseudo-Cushing syndrome.
Materials and Methods
Patients having performed a complete cortisol diurnal cycle in both serum and saliva during their hospitalization in Cochin Hospital Endocrinology department from 2012 to 2018 were included. Their clinical and biological characteristics were collected from Cochin electronic medical record. Pseudo-Cushing syndrome was diagnosed in patients with repeated biological anomalies but whose follow-up allowed the elimination of hypercortisolism. Serum and saliva cortisol during diurnal cycle were determined in competition immunoassays.
Results
466 patients were included in this study: 311 control subjects and 55 patients with pseudo-Cushing syndrome, grouped in "No-Cushing" ($n=366$); 73 patients with ACTH-dependent Cushing syndrome and 27 patients with cortisol-producing unilateral adrenal adenoma, grouped in "Cushing" ($n=100$). Salivary cortisol showed a good correlation with serum cortisol at all the times of the diurnal cycle (Spearman R ranging from 0.76 at 8 h to 0.88 at 20 h, $P<0.0011$). Considering the distinction between "Cushing" and "No-Cushing" groups; ^{24}H-cortisol level was expectedly the most discriminant parameter. ROC analysis of 24H-cortisol showed equivalent diagnostic performances in both saliva and serum (AUC = 0.95) giving a sensitivity of 89% and a specificity of 90% with a cut-off of **6.2** nmol/l and **175** nmol/l, respectively. Using these cut-offs, the proportion of false positive was > 20% in the pseudo-Cushing group, highlighting the difficulty of this differential diagnosis. Interestingly, the ratio maximal/minimal cortisol level during the day in serum allowed a good discrimination between pseudo-Cushing and ACTH-dependent Cushing syndrome groups, a cut-off of **3** giving a sensitivity of 86% and a specificity of 91% (AUC = 0.93). This ratio in saliva was less performant (AUC = 0.82).
Discussion
Saliva cortisol correlates well with serum cortisol at all the times of diurnal cycle; ^{24}H-saliva cortisol performing as well as 24H-serum cortisol for the positive diagnostic of Cushing syndrome. A ratio of maximal/minimal cortisol level in serum > 3 is highly predictive of pseudo-Cushing versus ACTH-dependent Cushing syndrome diagnosis.

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OC3.6

Venous thrombotic events (VTE) across ERCUSYN: details of these VTE's and do centres anticoagulate on a routine bases?

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For all ERCUSYN investigators
Background
Patients with Cushing's syndrome (CS) have an increased risk of developing venous thromboembolic complications. There is currently no standard practise for thromboprophylaxis in CS patients.
Aim
To study the details of VTE in patients included in The European Registry on Cushing's syndrome (ERCUSYN) and study various thromboprophylaxis protocols used among the centres where VTE's were reported.
Methods
A retrospective observational cohort study; data extraction from the registry was taken on the 07.02.2022. Additional data were requested for all VTE-positive cases and obtained in 93% of cases.
Results
There were 95 VTE among 2173 CS patients (prevalence of 4.4 %). Among the 57 centres included in the database, events were reported in 28. Details on VTE were available for 86 (88.4%) patients. One VTE was diagnosed in 69 patients, two VTE's in 9, and 3 VTE's in 6. All together there were 105 VTE. Deep venous thrombosis (DVT) was diagnosed in 50(47,6%) cases, pulmonary embolism (PE) in 29(27,6%) cases, other VTE in 21(20%) cases, and PE/DVT with VTE in uncommon locations or together were diagnosed in 5(4,8%) cases. At the time of the VTE only 30.4% were anticoagulated, on low-molecular-weight heparin (LMWH) (68%), vitamin-K antagonist (VKA) (24%), or on Xa-inhibitor 8%. Following the VTE 93.4% were anticoagulated, the agent used varying widely: 41% received VKA, 34.6% LMWH, 21.8% Xa inhibitor and 2.6% aspirin. The duration of anticoagulation varied from 2 weeks until lifelong (40%). Compression stockings were used in 50.9% of the VTE cases. Looking at the centre's routine thromboprophylaxis protocols, 43% anticoagulated on a routine basis. 8,3% anticoagulated only pituitary CS, 25% both pituitary and ectopic source CS and 66.7% anticoagulated all CS patients regardless of the aetiology. Anticoagulation schemes varied as far as anticoagulation initiation, the duration of thromboprophylaxis given and agent used; 25.6% anticoagulated preoperatively, 22.2% after confirmation of the diagnosis of CS, 33.3% only in particular situations: high-risk patients, following VTE or if medical therapy for hypercortisolism was started. In 75% of the centres LMWH was used, and less frequently VKA and Xa inhibitors.
Conclusion
We report a high VTE rate in CS patients within ERCUSYN. Most patients were not anticoagulated at the time of the event. There is no uniformly used thromboprophylaxis scheme in centres that reported VTE events. To our knowledge this is the largest registry-based study to date looking at VTE in CS patients.

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Oral Communications 4: Reproductive and Developmental Endocrinology

OC4.1

Gender-affirming hormone treatment: friend or foe? Long term follow-up of 755 transgender and gender diverse people

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Background
Gender-affirming hormone treatment (GAHT) is the cornerstone in the therapeutic management of transgender and gender diverse (TGD) people, which are currently classified as transgender assigned-female-at birth (t-AFAB) and assigned-male-at birth (t-AMAB) subjects. Due to its hormonal nature, GAHT is commonly handled by the endocrinologist and available guidelines on this topic mimic the recommendations for cis-gender hypogonadal populations. However, the GAHT long term management remains challenging, since the clinician must juggle a balance between achieving the phenotypic characteristics of the perceived gender and minimizing adverse effects. Although several longitudinal studies evaluated GAHT approaches, a focus on the challenges that the clinician should face off is still lacking.
Aim
Of the study: To investigate the long term therapeutic management of TGD people, considering hormonal targets, treatment adjustments and GAHT safety.
Methods
A retrospective, longitudinal, observational, multicentre clinical study was carried out, enrolling TGD subjects consecutively attending two Italian Endocrinology Units (Turin and Modena) from 2005 until 2022. Both t-AFAB and t-AMAB subjects were included, recording all data derived from routine outpatient evaluations. Each subject was managed with specific and personalized follow-up depending on the clinical practice of the Centre, as well as on the presence of adverse events, in accordance to the guidelines in force.
Results
Comprehensively, 302 t-AFAB and 453 t-AMAB were enrolled, showing similar follow-up average duration ($P=0.974$) and visits number ($P=0.384$). However, hormonal targets were reached more frequently in t-AFAB (63.6%) rather than in t-AMAB (23.3%) subjects. In addition, less time ($P=0.002$), fewer follow-up visits ($P=0.006$) and less changes in therapeutic schemes ($P=0.024$) were required in t-AFAB to achieve the therapeutic goal. Accordingly, t-AFAB showed

a higher adherence to medical prescriptions compared to t-AMAB subjects ($P<0.001$). During follow-up, the rate of both hypertension ($P=0.015$) and dyslipidaemia ($P<0.001$) increased in t-AFAB subjects, whereas t-AMAB ones showed a significant increase only in dyslipidaemia rate ($P<0.001$). No significantly increased rate of cardiovascular events was detected in both groups.
Discussion
Here, we described for the first time a long term follow-up during GAHT in a large cohort of Italian TGD people. This real-world clinical snapshot shows that hormonal balance is reached more frequently and more easily in transgender AFAB compared to AMAB subjects. Probably, these latter would require a thicker clinical management to overcome the higher intrinsic complexity of feminizing treatments, at least contributing to the poor therapeutic adherence observed in such subjects.

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OC4.2

Inhibition of RANKL in the testis increased the number of motile sperm in a sub-group of infertile men with preserved Sertoli cell function

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Currently, no treatment options exist to improve semen quality for the majority of infertile men. Proper interaction between germ and Sertoli cells in the testis is critical for sperm production, and a recent study suggested that Denosumab, an inhibitor of RANKL signaling, may stimulate sperm production in some infertile men. Here, we show in animal and human studies how expression of the RANKL signaling system is critical for both Sertoli cell function and the testicular response to Denosumab. RANKL was removed globally in mice using the Cre-LoxP system. qPCR and immunohistochemistry were used to investigate OPG expression in human testis with full spermatogenesis or Sertoli cell-only (SCO) syndrome, fetal testis, as well as cultures of human testis tissue treated with Denosumab. Reproductive hormones, semen quality, and anti-Müllerian hormone (AMH) levels were measured in 100 infertile men, who subsequently were randomized to a single subcutaneous injection with Denosumab (60 mg) or placebo (1 mL NaCl). After 80 and 160 days, semen samples were analyzed, and blood samples collected. Mice with global RANKL deletion had increased testicular and epididymal weight. OPG expression was high in Sertoli cells from human testis with SCO in contrast to testis with full spermatogenesis or fetal testis. In human testicular cultures with low or moderate OPG expression Denosumab increased germ cell proliferation and decreased apoptosis, while Denosumab had no effect in testis with spermatogenic arrest or high expression of OPG in Sertoli cells. In infertile men, low serum AMH was associated with poor Sertoli cell function and decreased semen quality. In the randomized placebo-controlled clinical trial one dose of Denosumab did not increase semen quality compared to placebo. However, in a sub-group of men with baseline serum AMH > 35 pmol/l Denosumab increased the inhibin B/FSH ratio and number of motile sperm cells, which is the best predictor of male fertility potential. This translational study suggests that the effect of Denosumab depends on the function of Sertoli cells with high OPG expression being a marker of dysfunction. AMH may be used to select the sub-group of infertile men who may benefit from Denosumab treatment; however, further investigation is critical for understanding the interplay between Sertoli cell function, spermatogenesis, and RANKL inhibition.

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OC4.3

The association between selected serum microRNAs, adipokine concentrations, and body composition assessed with dual-energy X-ray absorptiometry in young women with polycystic ovary syndrome

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Introduction
Polycystic ovary syndrome (PCOS) is associated with an increased risk of abdominal obesity, what is regulated by numerous genetic, epigenetic, and environmental factors. MicroRNAs (miRNAs) are known regulators of gene expression, involved in the development of metabolic disturbances. Dual-energy X-ray absorptiometry (DXA) is an accurate method of body composition analysis. The aim of the present study was to investigate the association between circulating miRNAs, adipokine concentrations, and body composition in PCOS patients.
Materials and methods
The studied group comprised 102 patients with PCOS (age: 24.3 ± 3.6 years; BMI: 24.7 ± 5.0) and 64 healthy women (age: 25.0 ± 3.4 years; BMI: 23.4 ± 3.7) as a control group. All women underwent anthropometric measurements, body composition analysis with DXA, and transvaginal ultrasound. Concentrations of sex hormones, sex hormone-binding globulin, adiponectin, leptin, lipids, as well as glucose and insulin during oral glucose tolerance test were measured. Serum levels of miR-27a, miR-106b, miR-181a, miR-193b, and miR-320 were assessed with real-time polymerase chain reaction.
Results
The studied groups did not differ in terms of age or BMI. No differences regarding body composition or the concentrations of leptin and adiponectin were observed. Expression levels of miR-27a and miR-193b were higher in PCOS patients, while miR-181a and miR-320 were higher in the control group (all $P<0.05$). In the PCOS group, significant correlations were observed between adiponectin concentration and the levels of miR-181a ($R=0.30$; $P=0.008$) and miR-320 ($R=0.24$, $P=0.031$), as well as between miR-106b and leptin concentration ($r=-0.25$; $P=0.045$). Additionally, the levels of miR-27a and miR-320 correlated with visceral adipose tissue (VAT) mass ($R=0.23$, $P=0.021$; $r=-0.25$, $P=0.013$, respectively) and android/gynoid (A/G) ratio ($R=0.25$, $P=0.011$; $r=-0.21$, $P=0.040$, respectively). The levels of miR-193b were associated with A/G ratio ($R=0.29$, $P=0.003$), fat mass index ($R=0.22$, $P=0.024$), and lean mass index ($R=0.32$, $P<0.001$). No such correlations were observed in healthy women, although in this group, miR-27a correlated with adiponectin concentration ($r=-0.37$, $P=0.010$), while miR-106b with leptin concentration ($R=0.34$, $P=0.046$) and fat free mass ($R=0.37$, $P=0.002$). In linear regression analysis, both miR-181a and miR-320 were associated with VAT mass independent of age, BMI, and waist circumference only in PCOS patients.
Conclusions
The expression levels of circulating miRNAs are altered in PCOS. Body composition, especially visceral adiposity, and adipokine secretion, seem to be associated with the expression of miR-27a, miR-181a, miR-193b, and miR-320 in this group, although functional studies are necessary to verify this hypothesis.

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OC4.4

A complex crosstalk between estrogen receptor β isoform signaling regulates human granulosa cell growth

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Estradiol (E2), produced by granulosa cells (GCs) of ovarian follicles, plays an essential role in folliculogenesis by controlling follicular development and selection. E2 actions are principally mediated by the two nuclear receptors, ERα and ERβ. These two receptors are differently expressed in GCs, with ERβ being predominant. After ligand binding and receptor dimerization, ERα and ERβ mainly regulate gene transcription through direct interaction with specific DNA motifs (estrogen-response elements, ERE), or by tethering onto other transcription factors such as c-Fos/c-Jun (activator protein-1, AP-1). In Human, four alternative splicing isoforms of ERβ (ERβ1, ERβ2, ERβ4 and ERβ5) are described and highly expressed in GCs. Little is known about their biological activities, except that only the longest form ERβ1 can bind E2. Therefore, the aim of our study was to identify the role of each ERβ isoform on GCs growth, as well as deciphering the nature of their respective transcriptional activities. For this purpose, we overexpressed each ERβ isoform in a human

immortalized GC line (HGrC1) to assess their respective role on cell proliferation and apoptosis. By scoring BrdU incorporation and measuring Annexin-V binding to membrane apoptotic proteins, we showed that ERβ2 and ERβ5 induced cell proliferation whereas ERβ1 and ERβ4 increased GCs apoptosis. Interestingly, transfection of ERβ isoforms in HGrC1 cells exhibited various effects on GCs fate, whether they were expressed alone or together. For example, pro-apoptotic activities of ERβ1 and ERβ4 were lost when both isoforms were co-expressed. To understand the underlying mechanisms of these effects, we examined ERβ transcriptional activities, with or without ligand, on luciferase reporter constructs driven by ERE or AP-1 dependent promoters. We found that only ERβ1 elicited ligand-dependent and ligand-independent transactivation at ERE sites. ERβ2, ERβ4 and ERβ5 (alone or together) did not influence ERβ1 transactivity. In addition, ERβ2, ERβ4 or ERβ5 showed a ligand-independent transactivation at AP-1 sites that impaired ERβ1 transactivity but led to gene transcription activation when all isoforms were co-transfected. In conclusion, our study demonstrates an important role of each ERβ isoform on GCs proliferation and apoptosis. Importantly, it reveals that although being E2-insensitive and unable to transactivate gene expression through ERE sites, ERβ2, ERβ4 and ERβ5 display biological effects. Their direct activities on AP1 sites as well as their potential non-genomic signaling are under current investigation. Hence, changes in the complex crosstalk between ERβ isoform signaling could contribute to uncontrolled cell growth such as that encountered in tumor cells.

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OC4.5

Reprogramming of reproductive signals via human luteinizing hormone/choriogonadotropin receptor (LHCGR)/G protein-coupled estrogen receptor (GPER) heteromers

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In the ovary, the G protein-coupled estrogen receptor (GPER) forms heteromeric complexes with the follicle-stimulating hormone receptor (FSHR), reprogramming FSH-induced signals and determining the follicular fate. Based on the structural similarity, we evaluated whether GPER interacts with the luteinizing hormone (LH)/choriogonadotropin (hCG) receptor (LHCGR) modulating gonadotropin-dependent signals. LHCGR-GPER heteromers were evaluated in transiently transfected HEK293 cells co-expressing specifically tagged receptors and biosensors, and signals were collected by bioluminescence resonance energy transfer (BRET) and photo-activated localization microscopy using photoactivatable dyes (PD-PALM). Cells were treated by LH/hCG and signalling analyses were performed by evaluating G proteins coupling and displacement, intracellular Ca2+, cAMP and inositol monophosphate (IP1) increase by BRET and homogeneous time-resolved fluorescence (HTRF). Activation of gene transcription regulated by nuclear factor of activated T-cells (*NFAT*) and cAMP response element (*CRE*) promoters was performed using a reporter system. Data were analysed by non-linear regression or Kruskal-Wallis test and Dunn's post-hoc test ($P<0.05$; $n=4$ to 6), as appropriate. Super-resolution microscopy revealed that about 20% of FLAG-GPER and HA-LHCGR form heteromers on the cell surface, and results were confirmed by BRET detecting yFP-GPER and rluc-LHCGR interaction ($r^2=0.91$; $n=6$). The presence of GPER induces concentration-dependent displacement of Gαq to LHCGR, resulting in depletion of hCG-induced Ca^{2+} response under GPER/lHCGR co-expression (AUC LHCGR= 5169±506 vs AUC LHCGR+GPER= 3621±277; $P<0.05$; $n=6$). Consistently, all other Gαq-dependent events, i.e. IP1 production (LH= 2.72±0.49 nM; hCG= 10.89±2.55 nM; $p\geq0.05$; $n=4$) and *NFAT* promoter activation (LHCGR LH= 2.4±0.3 vs LHCGR+GPER LH= 0.6±0.1; LHCGR hCG= 2.5±0.3 vs LHCGR+GPER hCG= 0.7±0.1; $n=5$; $P<0.05$), were inhibited in GPER/lHCGR co-expressing cells treated with LH/hCG. This is not in cells expressing LHCGR alone, where gonadotropins induced Gαq-dependent signalling ($P<0.05$; $n=6$). Interestingly, GPER-LHCGR complexes have no impact on LH/hCG-induced cAMP/protein kinase A (PKA) pathway activation ($p>0.05$; $n=6$), suggesting that GPER specifically inhibits Gαq-, but not Gαs-mediated signals. Control experiments were performed using a biosensor-tagged mutant GPER (GPERmut) unable to form heteromers with LHCGR. PD-PALM and BRET methods revealed the absence of GPERmut/lHCGR complexes and the lack of receptor-receptor interaction ($r^2=0.05$; $n=6$). Under these conditions, cell treatment with LH/hCG induced IP1 accumulation and gene transcription (LHCGR vs LHCGR+GPER; $P>0.05$; $n=5$). In conclusion, GPER interacts with LHCGR in the cell surface, biasing LH/hCG-induced signals via specific inhibition of Gαq-dependent cascades. These data suggest that reproductive functions may be modulated by GPER/lHCGR heteromers in the ovary.

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OC4.6

The severity of hot flashes is associated with the risk for incident metabolic syndrome and new-onset hypertension after the menopause

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Introduction

A growing body of evidence supports the possible association between the severity of climacteric symptoms and long-term cardiometabolic risk. We aimed to assess the possible link between the severity of hot flashes and the risk for cardiometabolic manifestations after the menopausal transition.

Methods

This cohort study was conducted in the Menopause Clinic, National and Kapodistrian University of Athens, Aretaieio Hospital, Athens, Greece. We reviewed outpatient records corresponding to 6,250 women, with no evidence of metabolic syndrome (MetSyn) at baseline and who were not on treatment with menopause hormone therapy (MHT) or selective estrogen modulators. Women should have had at least two full consultations 12 months apart. The eligible cases were matched one-two-one for age and the severity of hot flashes at baseline. We selected 825 women, stratified into three groups (no hot flashes vs mild vs moderate-to-severe). All participants were monitored for 15 years after their first visit (FU) for the development of MetSyn, new onset hypertension, and dyslipidemia.

Results

At the time of the first assessment, there was no association between the severity of hot flashes and the prevalence of hypertension and dyslipidemia (no vs mild vs moderate/severe: hypertension, 14.9% vs 20.9% vs 20.7%; dyslipidemia 8.4% vs 10.5% vs 6.9%). Women who experience severe symptoms at baseline had a higher prevalence of MetSyn and hypertension at 15-year follow-up (no vs mild vs moderate/severe, MetSyn 22.6% vs 17.1% vs 28.2%, $P=0.049$; hypertension, 26.9% vs 32.9% vs 38.9%, $P=0.025$). The time-to-diagnosis of MetSyn or hypertension was lower in women with more severe symptoms at baseline (KM curve, moderate/severe vs mild vs no, MetSyn 11.4±0.4 yrs vs 12.9±0.3 yrs vs 13.1±0.2 yrs; hypertension, 10.5±0.4 yrs vs 11.5±0.3 yrs vs 12.7±0.2 yrs; log-rank $P<0.001$ both cases). Cox-regression analysis showed that diagnosis of MetSyn was associated with moderate/severe hot flashes (HR=1.797, $P=0.021$), moderate alcohol consumption (HR=0.5, $P=0.003$), LDL-cholesterol (HR=1.007, $P=0.016$), intense exercise (HR=2.105, $P=0.048$), BMI (HR=1.095, $P=0.025$), age (HR=0.889, $P<0.001$). The diagnosis of hypertension was associated with moderate/severe hot flashes (HR=1.902, $P=0.004$), intense exercise (HR=2.276, $P=0.008$), current smoking (HR=1.664, $P=0.008$), moderate alcohol intake (HR=0.439, $P<0.001$), SBP (HR=1.029, $P<0.001$), BMI (HR=1.1, $P=0.007$), age (HR=0.888, $P<0.001$). The models were also adjusted for waist circumference, HOMA-IR, lipids, DBP.

Conclusions

Moderate-to-severe hot flashes were associated with incident risk for MetSyn and new-onset hypertension in young postmenopausal women. These observations bear implications for the use of MHT in women shortly after the menopausal transition.

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Oral Communications 5: Adrenal and Cardiovascular Endocrinology 1

OC5.1

CYP21A2-R484Q mice, a humanized mutant animal model for congenital adrenal hyperplasia

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Congenital Adrenal hyperplasia (CAH) refers to a group of autosomal-recessive inherited disorders of impaired adrenal steroidogenesis. The most common form is 21-hydroxylase deficiency (21-OHD) caused by mutations in the *CYP21A2* gene. Patients lack glucocorticoids and in some cases mineralocorticoids, and present with androgen excess causing hypoglycemia, live-threatening salt wasting, virilisation, and precocious puberty. Treatment includes the replacement of deficient steroid hormones and restoring negative feedback towards CRH and pituitary ACTH secretion to suppress hyperandrogenemia. This often requires the administration of supra-physiological doses of glucocorticoids which may cause significant treatment-related side effects. As recent advances have shed light on the steroidogenic mechanisms and the genetics of CAH, multiple novel treatment approaches are being developed to holistically manage CAH patients, to minimize glucocorticoid exposure and to achieve better patient outcomes. However, novel drugs lack effective *in-vivo* models for pre-clinical testing. In this work, we present the first viable and humanized mouse model in which the mouse gene *Cyp21a1* is replaced by the human orthologue *CYP21A2* with the integrated human point mutation p.R484Q. Twenty-weeks-old homozygous mice showed hyperplastic adrenals and an expression of the human *CYP21A2* gene. Tandem mass spectrometry measurements of plasma at 20 weeks showed decreased corticosterone and 11-deoxycorticosterone levels in both male and female homozygous animals. Additionally, progesterone levels in homozygous mice were significantly higher ($P<0.01$) than in wildtype mice. We also observed increased aldosterone levels in female mutants, whereas blood pressure did not differ between wildtype and mutant mice strains. ACTH levels were elevated in both male and female homozygous animals. Tetrahydrocorticosterone (THB), a major glucocorticoid metabolite could be detected in 24-hours-urine in wildtype mice but not in homozygous mutant animals. While mutant male mice were fertile with normal appearing testes, females were infertile, remaining in the diestrus phase with a reduced number of ovarian follicles. In conclusion, we show that the humanized mutant *CYP21A2* mice may represent an excellent animal CAH model to test novel treatment strategies. It will potentially contribute to achieving overarching treatment goals to prevent comorbidities resulting from hormone – related derangements and treatment-related side effects among CAH patients. The animal model will play a pivotal role in supporting the transition from basic research to clinical application.
Keywords: Adrenals, CAH, animal models

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OC5.2

The association between hormonal control during infancy and testicular adrenal rest tumor development in males with congenital adrenal hyperplasia

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Background
Testicular Adrenal Rest Tumors (TART) in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency (21OHD) or 11-hydroxylase deficiency (11OHD) are benign lesions causing testicular damage and infertility. We hypothesize that high ACTH exposure due to poor hormonal control during early life is promoting development of TART later in life.
Objective
This study aims to examine the relation between early CAH diagnosis and consequent start of adequate glucocorticoid treatment (<1 month vs>1 month but<1 year vs>1 year) ánd the development of TART as well as the relationship between biochemical disease control during infancy and early childhood and the development of TART.
Methods
In this retrospective open cohort study, data was collected from the I-CAH registry; an international database of pseudonymized information on CAH patients. The study included 189 male patients from 22 centers with 21OHD ($n=182$) or 11OHD ($n=7$) in which at least one testicular ultrasound (US) was performed.
Results
TART was detected by US in 38% of the patients. Prevalence varied enormously between centers. Salt-wasting phenotype was associated with a 3.2 (confidence interval: 1.1-9.0) times higher risk of TART diagnosis compared to simple virilizing phenotype. When adjusted for CAH phenotype, a delayed CAH diagnosis of more than 1 year, compared to a diagnosis within 1 month of life, was associated with a 2.4 (1.3-4.7) times higher risk of TART diagnosis later in life. Biochemical disease control (undertreatment versus adequate treatment or overtreatment) or bone age advancement (as a consequence of poor disease control) in the four yearly visits did not predict TART diagnosis later in life. Increased height SDS at the end of the four-year follow-up period, but not at earlier visits, was associated with a 1.3 (1.1-1.5) times higher risk of TART diagnosis later in life.
Conclusion
A delayed CAH diagnosis of more than 1 year versus CAH diagnosis within 1 month of life is associated with a higher risk of TART development, what might be attributed to high ACTH exposure of the neonatal testes. However, the relation between a delayed CAH diagnosis and TART diagnosis may be confounded by a potential link between delayed CAH diagnosis and experience in and quality of CAH care. The number of patients per center did not allow for normalization of potential center-specific effects. Nonetheless, neonatal screening may help improving CAH treatment and lower the risk of TART development later in life.
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OC5.3

Switching patients with Congenital Adrenal Hyperplasia to Modified release hydrocortisone capsules: relative bioavailability and disease control

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Background
Modified-release hydrocortisone (MRHC) capsules (Efmody, Diurnal Ltd, Cardiff, UK), have been developed to replicate the cortisol diurnal rhythm and shown to improve CAH disease control1. We have examined relative bioavailability of MRHC and disease control of congenital adrenal hyperplasia (CAH) patients switched from standard therapy to MRHC.
Methods
An open label, randomised, 2 period, crossover study comparing the relative bioavailability of MRHC capsules with immediate-release hydrocortisone tablets (Cortef, Pfizer) in dexamethasone-suppressed healthy volunteers was performed (NCT03343327). The Primary Endpoint was area under the cortisol concentration time curve extrapolated to infinity ($AUC_{0\text{-inf}}$), with bioequivalence considered met if the ratio $AUC_{0\text{-inf}}$ was between 80-125%. For disease control in classic CAH patients switched to MRHC, we reviewed data from the phase 3 randomised study of standard treatment versus MRHC (NCT02716818). Patients were randomised either to continue standard treatment or switched to MRHC at the same hydrocortisone dose equivalent (HDE = prednisolone dose × 5; dexamethasone × 80)[1]. Patients were assessed at baseline and after 4 weeks by 24 hr 2-hourly sampling of 17-hydroxyprogesterone (17OHP) with change from baseline in the natural log 24 hr 17OHP standard deviation score (SDS) profile calculated (17OHP SDS 24-hour profile).
Results
24 subjects completed the relative bioavailability study. 20 mg MRHC capsules showed AUC bioequivalence to 20 mg reference hydrocortisone: Mean $AUC_{0\text{-inf}}$ was 2650 vs 2450 h × nmol/l, ratio of 108% (90% confidence interval (CI) 103 – 113%). In the phase 3 study, 122 patients were recruited of which 105 were included in the 4-week analysis; standard treatment ($n = 52$) MRHC at the same dose as standard treatment ($n = 53$). The mean 9am 17OHP at baseline vs 4 weeks was: 41 vs 6 (nmol/l) for the MRHC group and 21 vs 18 (nmol/l) in the standard treatment group. At 4 weeks, a greater reduction in the 17OHP SDS 24-hour profile was observed in the MR-HC group than the standard therapy group; treatment effect (90% CI) −0.26 (-0.46 to −0.07), $P = 0.007$. There were no adrenal crises in the MRHC group and 3 in the standard treatment group for the whole phase 3 cohort over 6 months.
Conclusions
MRHC capsules are bioequivalent to immediate release hydrocortisone for AUC, however the more physiological exposure means that switching patients from standard treatment to MRHC at the same hydrocortisone dose equivalent results in improved CAH control. The incidence of adrenal crisis on MRHC is at the lower end of that reported in cohort studies.
Reference
1. Merke DP., JCEM 2021 106 e2063-e2077.

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OC5.4

Adrenal Insufficiency Associated with Biallelic Mutations in Porphyria Genes

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Adrenal insufficiency (AI) is life-threatening and can present alone or in combination with other co-morbidities. Here we describe families with a novel association of AI with porphyria caused by biallelic mutations in protoporphyrinogen oxidase (*PPOX*) or coproporphyrinogen oxidase (*CPOX*). The porphyrias are a group of disorders caused by defects in one of eight enzymes within the haem biosynthetic pathway, divided into acute porphyrias, resulting in mainly neurovisceral symptoms, or cutaneous porphyrias, mainly affecting the skin. Acute porphyria attacks can be life-threatening, resulting in permanent disability or death. Variegate porphyria and hereditary coproporphyria are associated with autosomal dominant mutations in *PPOX* and *CPOX* respectively, with biallelic inheritance rarely reported and knockout mice that are embryonic lethal. We performed whole exome sequencing (WES), array Comparative Genomic Hybridization (aCGH) and whole genome sequencing (WGS) in 3 families with AI and variegate or hereditary porphyria. In kindred 1, with 4 affected individuals, WES revealed a homozygous mutation, p.Glu339Lys, in *PPOX*. aCGH and WGS revealed no Copy Number Variants (CNVs) and no other variants, in genes causing AI, common to all affected individuals. In families 2 and 3, homozygous mutations in *CPOX* p.(Pro367Ala) in one patient and p.(Ser28Ter) in two siblings were identified by WGS and WES respectively, with a clinical picture of AI and hereditary coproporphyria. Unlike other acute porphyria kindreds, the heterozygous parents were asymptomatic, manifesting neither porphyria nor AI, suggesting that the level of enzyme function is key for both phenotypes. Reduced PPOX/CPOX activity could cause AI through either; (i) a dearth of haem for steroidogenic CYP450 enzyme action, (ii) toxicity of intermediate porphyrins or (iii) increased oxidative stress. To investigate the mechanism, we first created H295R, human adrenocortical cells, with differing degrees of *PPOX*-knockdown (KD) by shRNA. Proliferation, measured by MTT assay or GFP accumulation, was lower in *PPOX*-KD cells at 72 hours and mitochondrial respiration was diminished, possibly due to toxicity of porphyrin precursors. *CYP11A1* expression was unaltered whereas *STAR* and *CYP17A1* were significantly lower in *PPOX*-KD cells. Finally, and definitively, knockdown of at least 60% PPOX protein in H295R cells reduced cortisol output by 2.2-fold ($P < 0.01$) at baseline and 1.9-fold ($P < 0.0001$) in forskolin stimulated cells. Similar *CPOX* studies are underway. These studies show that cortisol is reduced in individuals with biallelic *PPOX/CPOX* mutations and, in conjunction with previous cases of AI in association with other genes in the pathway, suggests adrenal function should be monitored in individuals with porphyria.

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OC5.5

Moving to liquid chromatography-tandem mass spectrometry to assess hypercortisolism states through dexamethasone suppression test: comparison with two routinely used immunoassays

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Background
The dexamethasone suppression test (DST) is among essential tests for hypercortisolism diagnosis. Due to high sensitivity and specificity, liquid chromatography-tandem mass spectrometry (LC-MS/MS) is replacing obsolete immunoassays (IA) for steroid measurement. However, exhaustive data about IA and LC-MS/MS concordance in the frame of DST are still not available.
Aim
To compare cortisol measurements by two routine IAs and LC-MS/MS in basal (F0) and post-DST (Fdst) sera. To assess between-method concordance in diagnosing hypercortisolism.
Methods
We enrolled 330 patients with hypercortisolism suspicion or adrenal mass. Of these, 287 patients had their paired F0 and Fdst measured by ElecsysE170 (Roche), and 43 by DxI800 (Beckman). All samples were also measured by a validated LC-MS/MS method. Methods were compared by Wilcoxon test and Passing and Bablok regression. We evaluated between-methods concordance in classifying patients in "non-secreting" (NS) (Fdst < 18 ng/ml), "possible autonomous cortisol secretion" (PACS) (Fdst:18-50 ng/ml) and "autonomous cortisol secretion" (ACS) (Fdst ≥ 50 ng/ml).
Results
F0 levels assayed by ElecsysE170 (median (min-max): 151.0 (47.0-380.0) ng/ml) were significantly higher than by LC-MS/MS (116.8 (38.1-249.5) ng/ml)) ($P < 0.001$), with significant proportional overestimation (slope(95CI): 1.366(1.309-1.423)) and constant underestimation (intercept(95CI): −7.9(-14.1–1.8)) of the former and $R = 0.916$. Comparing DxI800 vs LC-MS/MS resulted in higher values (134.0 (52.0-269.0) ng/ml vs 115.1 (55.3-207.8) ng/ml, respectively) ($P < 0.001$), significant slope (1.337(1.226-1.451)) and intercept (-18.6(-33,3–7.3)) and $R = 0.955$. Regarding Fdst levels, no significant differences were found between ElecsysE170 (14.0 (3.00-290.0) ng/ml) and LC-MS/MS (13.70 (2.72-168.7) ng/ml) ($P = 0.060$), with no significant proportional or

constant errors and $R=0.907$. No difference was obtained for DxI800 (14.0 (6.0-258.0) ng/ml) vs LC-MS/MS (13.3 (6.9-199.0) ng/ml) ($P=0.160$), with no proportional error, $R=0.910$, and a small significant constant underestimation (intercept: −2.8; 95CI: −4.9–0.7). According to ElecsysE170, we classified 186 patients (64.8%) as NS, 88 (30.7%) as PACS and 13 (4.5%) as ACS. When using LC-MS/MS, 13 (7%, false negatives) of NS, 19 (21.6%, false positives) of PACS and 3 (23.1%, false positives) of ACS were not confirmed, with total 35 (12.2%) misdiagnoses. When using DxI800 Fdst, 26 (60.5%) were NS, 14 (32.5%) were PACS and 3 (7.0%) were ACS. Of these, LC-MS/MS did not confirm 1 (3.8%, false negative) within NS and 1 case (33.3%, false positive) within ACS classes, with total 2 (4.7%) misdiagnoses.
Conclusions
Unexpectedly, concordance between LC-MS/MS and IAs is poorer at basal than DST-suppressed cortisol levels. Nonetheless, a non-negligible amount of patients may receive a different diagnosis when using the more specific and accurate LC-MS/MS measurement.

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OC5.6

Venous thromboembolism complications in Cushing's syndrome: results of a secondary survey within the European Registries for Rare Endocrine Conditions (EuRRECa) and the European Reference Network on Rare Endocrine Conditions (Endo-ERN)

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Background
Venous thromboembolism(VTE) is a well-known perioperative complication in patients with Cushing's syndrome(CS) and may be preventable. A recent report highlighted that thromboprophylaxis management in patients with CS still varies considerably across Endo-ERN reference centers but the actual incidence of VTE and its management in individual patients is unclear.
Aim
To collect epidemiological and clinical data of new cases of CS reported on the European Registries for Rare Endocrine Conditions(EuRRECa) electronic reporting tool(e-REC) and Endo-ERN.
Methods
A survey was conducted for new patients with CS reported by e-REC by reference centers within Endo-ERN in the last 2 years. A total of 180 patients were reported with CS and the survey was completed by 26 clinicians in 11 centres in 6 countries. Risk factors, VTE occurrence, and thromboprophylaxis regimens were analysed.
Results
One hundred and thirteen patients had Cushing disease (62.8%), 59 CS (32.3%) and 8 patients ectopic CS (4.4%). 136 (75.6%) were female with a mean age of 45 ± 16.2 years (range 3-80). Overweight (BMI 25-30 kg/m^2) and obesity (BMI ≥30 kg/m^2) were common findings with 78 (43.3%) and 61 (33.9%) patients respectively. 121 had hypertension (67.2%), 38 had diabetes mellitus (21.1%). 11 patients reported VTE(6.1%) prior to CS diagnosis. Medical treatment of CS consisted of metyrapone ($n=50$, 27.8%), ketoconazole ($n=16$, 8.9%), osilodrostat ($n=3$;1.7%), and mitotane ($n=1$, 0.56%). One hundred and twelve patients (64.4%) did not receive cortisol lowering treatment before surgery. CS was completely controlled in 35 patients (19.4%) and partially in 31 (17.2%) before surgery. Most patients were operated ($n=167$, 92.8%), first surgery in 76.6% of patients. 136 patients received thromboprophylaxis before surgery, mostly using Low-molecular weight-heparins (94.2%). In 42 cases, thromboprophylaxis was started the day of surgery (30.4%), in 51 stopped within one week after surgery (36.9%). VTE was reported in only 4 cases (2.2%), all of them in uncontrolled CS. Of these, 3 VTE's occurred months before surgery, in patients with history of VTE and high VTE risk, 2 of them developing VTE while on anticoagulant treatment for previous VTE. Only 1 VTE occurred after surgery(6 weeks) in a patient who received thromboprophylaxis the first week after surgery. No severe bleeds were observed during thromboprophylaxis.
Conclusion
The results of this survey suggest a heterogenous policy on pre-surgery cortisol lowering treatment and thromboprophylaxis. In this survey VTE's were only observed in subjects without cortisol lowering therapy and with additional VTE risks. In addition, we observed no major bleeds in patients on thromboprophylaxis. Therefore this survey paves the way for the standardization of thromboprophylaxis regimens in subjects with CS.

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Oral Communications 6: Endocrine-related Cancer

OC6.1

RNA splicing landscape of pancreatic neuroendocrine neoplasms reveal novel clinico-molecular associations

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Neuroendocrine neoplasms (NENs) are a highly heterogeneous group of tumors that arise from the diffuse neuroendocrine system and whose incidence has increased over the last years. Among them, pancreatic NENs (PanNENs) are relatively common and one of the most studied NENs. PanNENs are characterized by a low number of mutations, with some genes frequently mutated, such as *MEN1*, *ATRX*/*DAXX*, and mTOR signaling pathway genes. Despite genomics, transcriptomics and epigenomics studies that have helped improved understanding of the molecular features of PanNENs, there is still vast unexplored ground for better comprehension of this disease. In this context, the process of RNA splicing, which is the removal of introns from pre-RNA molecules, is known to be dysregulated in many diseases and it has even been shown to contribute to every hallmark of cancer. Our group has previously demonstrated that RNA splicing is also dysregulated in PanNENs, where it opens up new therapeutic avenues. However, clinical and molecular implications of this dysregulation are still very poorly understood. In this work, we aimed to describe the spliceosomic landscape, that sums alternative splice variants, events and splicing machinery components expression, as well as their potential relationship, how it is related to the pathology of PanNENs and its contribution to their high heterogeneity, tumorigenesis and behavior. With this aim, we explored two different cohorts of 175 and 66 PanNENs samples, including RNA-seq, mutational and clinicopathological data, integrated to better understand the disease. The expression levels of splicing variants/events and splicing machinery components in each sample were quantified using SUPPA-2 and DESeq-2, respectively. We used dimensionality reduction techniques to classify samples according to their spliceosomic landscape and later explored their relationship with pathological and mutational data. Results revealed important associations between clinical data, such as hormone secretion (tumor functionality), tumor grade or metastasis, and specific splicing profiles, implying a relevant role of alternative splicing in PanNENs pathophysiology. Additionally, the most common mutations in PanNENs showed specific splicing landscapes. Further analysis and experiments will be required to ascertain whether splicing alterations are merely a subsidiary effector of hierarchically higher molecular changes or, contrarily, function as tumor drivers. In conclusion, our study represents the first spliceosomic study in PanNENs and provides original information to better understand the heterogeneity and pathophysiology of these tumors.

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OC6.2

Aminoacyl-tRNA synthetases as diagnostic, prognostic, and therapeutic tools in MAFLD-derived hepatocellular carcinoma

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Metabolic dysfunction-associated fatty liver disease (MAFLD) is a growing cause of hepatocellular carcinoma (HCCs); however, the molecular characteristics of MAFLD-derived HCCs are still to be elucidated. To provide novel insights in this field, we performed the first quantitative proteomic analysis of HCC samples from different aetiologies. Particularly, cytosolic and nuclear proteome of liver tissues from HCC patients ($n=42$; HCC vs adjacent tissue) and healthy controls ($n=5$) were determined by SWATH-MS-based proteomics. This proteomic profile allowed for the discrimination of two tumoral subgroups. One of them, which included all the MAFLD-derived HCC patients, was associated to aggressive parameters and to a profound dysregulation of the aminoacyl-tRNA synthetases (ARSs), which are essential components of the tRNA aminoacylation machinery. The alteration of the 9 ARSs dysregulated in the proteomic cohort was confirmed in different *in silico* MAFLD and HCC cohorts, wherein they were associated to aggressive features (i.e., survival and recurrence), and to the metabolic status of the patients (i.e., obesity). Indeed, the general upregulation of the ARSs machinery was identified as a prognostic marker in different mRNA and protein cohorts in that HCC patients with high expression of ARSs had worse survival and a higher recurrence. The valine tRNA-aminoacyl synthetase, VARS1, was selected for studying the functional and molecular consequences of ARSs dysregulation in HCC as its expression was altered in most HCC cohorts and associated to the presence of obesity. For that, *in vitro* assays (proliferation, migration, colonies/tumorspheres) were performed in liver cancer cell lines (HepG2, Hep3B, SNU-387) after the modulation of the expression (silencing and overexpressing) of *VARS1*. VARS1 modulation had a reduced effect on proliferation/migration although it significantly altered the dedifferentiation capacity of the cells (colony establishment and spheres formation). The molecular mechanism underlying this effect was assessed through quantitative proteomics in Hep3B and SNU-387 cell lines after overexpressing *VARS1*. This analysis (and further confirmation by western blot) demonstrated a decreased expression of the scaffold protein *MAGI-1*, a known tumour suppressor in HCC, associated with the overexpression of *VARS1*. Thus, VARS1 might be exerting its role through the modulation of MAGI-1-mediated cell junctions. Our study demonstrates the dysregulation of the tRNA-aminoacylation machinery as a diagnostic and prognostic marker in MAFLD and HCC and the potential of these proteins, especially VARS1, as therapeutic targets in tumoral stages.

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OC6.3

Tumor microenvironment of adrenocortical carcinoma dissected by single-cell RNA-sequencing

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Background

Molecular classification is important for diagnosis and prognosis of adrenocortical tumors (ACT). Transcriptome profiles separate benign ACT ("C2" cluster) from carcinomas (ACC) and identify two groups of ACC, "C1A" ("steroid" and "proliferation" signatures) and "C1B" ("immune" signature), of poor and better prognosis respectively. However, these signatures were characterized at the tissue level ("bulk") and our knowledge of the cellular composition of ACC is limited. The aim of this study was to dissect the tumor microenvironment composition in "C1A" and "C1B" ACC.

Methods

We performed single-nuclei RNA-sequencing (10×) of ~170,000 cells from human normal adrenal ($n=4$), benign ACT ($n=14$) and ACC ($n=20$). Bioinformatic analyses were conducted using CellRanger and Seurat pipelines to construct a single-cell atlas of normal and tumoral adrenal cortex. This atlas was then used to estimate the cell proportions (Cibersortx) in "bulk" transcriptome data of 216 ACC patients: a microarray dataset (ENSAT 2014, $n=46$), a full-length RNA-sequencing dataset (TCGA, $n=78$) and a 3' RNA-sequencing dataset (ENSAT 2021, $n=92$). Finally, we tested the association of tumor microenvironment composition with hormone secretion and outcome.

Results

Microenvironment of steroid cells was composed of fibroblasts (4.6% of total cells), endothelial cells (5.1%), myeloid cells (9.9%) and lymphoid cells (1.3%). Comparing "C1A" and "C1B", only minor differences were observed for proportions of fibroblasts (2.4% and 2.8% respectively, $P<0.001$), endothelial cells (4.0% and 3.3%, $P<0.001$) and myeloid cells (10.4% and 13.3%, $P<0.001$). In ACC microenvironment, fibroblasts, endothelial cells and myeloid cells corresponded mainly to cancer-associated fibroblasts (expressing *PDGFRB* and *FN1*), tumor-associated endothelial cells (expressing *ANGPT2* and *VWF*) and tumor-associated macrophages (expressing *CD163* and *F13A1*) respectively. Comparing "C1A" and "C1B", a subpopulation of immune cells was enriched in "C1B" ACC. Deconvolution in bulk transcriptomes showed that this population is associated with non-cortisol secreting tumors (t-test $P=0.002$, $P<0.001$ and $P=0.03$), longer disease-free survival (Logrank $P=0.006$, $P<0.001$ and $P<0.001$) and longer overall survival (Logrank $P=0.004$, $P=0.006$ and $P<0.001$ in ENSAT 2014, TCGA and ENSAT 2021 datasets respectively).

Conclusion

A specific population of immune cells may be repressed by glucocorticoid secretion, leading to immune system escape in poor prognosis "C1A" ACC. This may impact immunotherapy strategies in this cancer.

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OC6.4

CAR-T cell therapy exerts effective antitumor efficacy under immunosuppressive conditions in adrenocortical carcinoma

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Background

Adrenocortical carcinoma (ACC) is a very rare and aggressive, endocrine malignancy with still limited treatment options. Approximately 60% of patients with ACC show endogenous glucocorticoid excess which could be one potential cause, why first clinical trials with immunotherapies, like immune checkpoint inhibitors, showed only modest results. Due to the lack of an ACC-specific antigen structure, other immunotherapeutic approaches, like specialized cancer treatments using chimeric antigen receptor (CAR) therapy in ACC, have not been tested so far. In this study, we evaluated the expression of a new enticing tumor antigen (TA*) structure and investigated the effect of TA-specific CAR-T cells *in vitro*.

Methods

TA expression has been initially evaluated at mRNA level by qRT-PCR and at the protein level by qFACS analysis in five human ACC cell lines. TA mRNA expression has been investigated in 54 adrenocortical tissues (13 normal adrenal glands (nAG) and 41 ACC samples). Chromogenic immunohistochemistry (IHC) was assessed in 135 paraffin-embedded ACC tissues. In addition, RNAscope single cell analyses in an IHC subcohort of 30 ACC tumor samples was performed. At last, functional testing was conducted for four different TA-specific CAR-T cell modifications, including proliferation, tumor killing and cytokine release.

Results

All five ACC cell lines express the investigated TA. TA expression at mRNA level was present in 60.92% and at protein level at 75.56% of all ACC samples. TA expression was significantly higher in ACC compared to nAG (0.00 vs 0.0015, $P=0.0146$) and in metastasis more than primary tumors (0,0021 vs 0,0060, $P=0.0020$). High TA mRNA levels were also strongly associated with glucocorticoid excess, (0.0066 vs 0.0010, $P=0.0341$) ENSAT tumor stage (0.0032 vs 0.0005, $P=0.0091$) and sex (0.0012 vs 0.0039, $P=0.0237$). Furthermore, RNAscope single cell analysis revealed fairly homogenous TA expression in ACC. *In vitro* treatment showed effective cytotoxic effects of TA-specific CAR-T cells in cell lines (74.9% specific lysis of NCI-H295R cells, E-T 1:1) and primary tumor cells as well as CAR-T cell proliferation upon antigen contact and cytokine release in all five TA positive cell lines.

Conclusions

Our preliminary results showed that the investigated TA is sufficiently and fairly homogenous expressed in human ACC specimens and that TA-specific CAR-T cells exert effective antitumor efficacy under immunosuppressive conditions on ACC cells *in vitro*.

Key words: CAR-T cell therapy, adrenocortical carcinoma, glucocorticoids, immunotherapy

*The evaluated ACC-specific tumor antigen is kept confidential for the time being for patent law reasons

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OC6.5

WEE1 kinase inhibitor, adavosertib (AZD1775), as a novel potential therapeutic strategy in advanced adrenocortical carcinoma

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Background
Adrenocortical cancer (ACC) is a rare malignant neoplasm with a dismal prognosis, particularly in advanced disease. For these patients only limited therapeutic options are available. Adavosertib (AZD1775) is a potent inhibitor of tyrosine kinase WEE1 that regulates cell cycle checkpoints, slowing cell cycle progression and leading to mitotic entry in the presence of DNA damage. Therefore, its use could potentiate existing DNA damage-based therapies. Here, we evaluate the expression of WEE1 in ACC tissues and ACC cell lines and investigate the effect of adavosertib alone or in combination with cisplatin or gemcitabine *in vitro*.
Methods
WEE1 mRNA expression has been evaluated in 91 adrenocortical tissues (19 normal adrenal glands/NAG; 20 adenomas/ACA; 52 ACC) and 5 available ACC cell lines. Immunohistochemistry was assessed in 114 paraffin-embedded ACC tissues (with known *TP53* mutation status) and evaluated by automated image analysis. WEE1 expression was correlated with clinical outcome. In vitro cell viability was evaluated by CellTiter-Glo assay following exposure of cells for 96h to increasing concentrations of adavosertib alone or in combination with cisplatin or gemcitabine according to the Chou and Talalay method. Cell apoptosis and cell cycle were analyzed by flow cytometry.
Results
WEE1 levels were significantly higher in ACC compared to NAG (0.032 vs 0.012, respectively, $P=0.04$) but not to ACA. Low WEE1 mRNA levels were associated with better overall survival (HR 0.32, 95% CI 0.12-0.86, $P=0.02$), independently of established prognostic factors, whereas only a trend was observed at protein level (HR 0.31, 95% CI 0.07-1.26, $P=0.10$). WEE1 staining was significantly higher in *TP53* mutated ACC ($n=34$) compared to wild type ($n=80$; median score 97 vs 72, $P<0.001$). Exposure of NCI-H295R, JIL-2266 and CU-ACC2 cells to adavosertib induced cytotoxicity with IC50 of 1.17, 1.35 and 0.4 μM, respectively. CU-ACC1 and MUC-1 showed less sensitivity to adavosertib alone, but its effect was enhanced by cisplatin and gemcitabine and this additive-synergic effect was observed in all cell lines. Upon 48h of treatment with adavosertib alone (1.25 μM), all cell lines showed an increased frequency of dead cells and apoptotic cells with enrichment of cells in the S phase, compared to the DMSO control.
Conclusion
Our results showed high WEE1 expression in ACC tissue and cell lines. WEE1-inhibitor adavosertib exerts a cytotoxic effect on ACC cells inducing apoptosis and cell cycle perturbation. Cisplatin and gemcitabine, commonly used in ACC treatment, enhanced the adavosertib effect, giving a new pharmacological option in ACC over standard therapies.

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OC6.6

Cellular landscape of adrenocortical carcinomas determined by molecular profiling of primary, recurrent and metastatic tumour samples at single-nuclei resolution.

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Background
Molecular mechanisms of malignant adrenocortical tumorigenesis remain elusive despite previous comprehensive genomic studies. Nonetheless, cellular heterogeneity of primary, recurrent and metastatic adrenocortical carcinoma (ACC) haven't been fully investigated.
Aim
To characterize the molecular profile of different cell subtypes in primary, recurrent and metastatic ACC by single-nuclei RNA sequencing (snRNA-Seq), using adult human normal adrenal glands (NAG, $n=6$) and adrenocortical adenomas (ACA, $n=12$) as reference.
Methods
Single nuclei were isolated from 14 ACC samples, including 6 primary tumours, 3 local recurrence and 5 ACC metastasis from 9 different patients. Genomic alterations were evaluated by targeted next-generation sequencing in 6 cases, whereas *CTNNB1* mutation were excluded by Sanger sequencing in the remaining 3 cases. snRNA-Seq was performed using 1CellBio. Seurat R package was used for data analysis, integration and exploration. Integration of datasets was performed by anchor pairs between ACC and NAG. Identification of cell subpopulations was performed using unsupervised clustering followed by differential gene expression analysis, with cluster annotation based on marker genes and scores for hallmark gene sets or the gene signatures of previously identified ACA cell populations.
Results
The ACC tumour microenvironment was relatively devoid of immune cells compared to NAG, emphasising that ACC is an immunological cold tumour. The integrated analysis revealed the presence of 7 subpopulations of cortical-derived cells in ACC. Among these, ACC recurrence and metastasis were highly represented by a cell population overexpressing *IGF2*, *DLK1*, and the translationally controlled tumour protein *TPT1*, and significant enrichment of ribosomal biogenesis and proliferation-associated signalling pathways. A second major subpopulation, enriched within primary ACC samples, displayed a transcriptional signature of increased cholesterol homeostasis and steroid synthesis similar to that observed in our cortisol-producing ACA. The intra-tumour differential gene expression analysis revealed that a decrease in expression of steroid hormone production genes, an upregulated cellular proliferation, an increased expression of *IGF2, DLK1, TPT1* as well as the silencing of *MEG3* and *MEG8* are distinguishing ACC from NAG/ACA cells. Cortical cells statistically indistinguishable from NAG made up the remaining bulk of the ACC cell population, while smaller subpopulations were highly enriched with cell cycle genes or characterized by *ACSM3*, *KRTCAP2* or *ZNF331*.
Conclusion
Our analyses represent the first molecular characterization of ACC at single-nuclei level, allowing the investigation of the molecular heterogeneity of ACC. The transcriptomic signatures showed the presence of 7 different subpopulations, including a specific cell population overexpressing *IGF2, DLK1* and *TPT1* associated to recurrent and metastatic ACC.

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Oral Communications 7: Pituitary and Neuroendocrinology 2

OC7.1

Investigating intranasal kisspeptin as a novel, effective and preferable route of delivery using human, rodent and pharmaceutical models

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Background
Kisspeptin is a critical activator of hypothalamic GnRH neurons and is essential for reproductive health. Emerging data reveals that kisspeptin-based therapeutics have substantial potential to treat reproductive, psychosexual and bone disorders. However, current delivery is limited to the subcutaneous or intravenous routes, presenting barriers to development. Alternative routes of administration would

overcome this and capitalise on the benefits of kisspeptin-based therapies. To address this, we comprehensively investigated the therapeutic potential of intranasal kisspeptin administration for the first time using a series of human, rodent and pharmaceutical studies.

Methods

Human studies: Healthy men ($n=12$) and a patient group of women with hypogonadism (due to Hypothalamic Amenorrhoea [HA], $n=5$) completed a randomised, double-blind, crossover, placebo-controlled study investigating the acute effects of intranasal kisspeptin-54 administration vs 0.9% saline placebo. After monitored self-administration of intranasal kisspeptin (doses: 3.2-25.6 nmol/kg [healthy men] and 12.8 nmol/kg [women with HA]) or placebo, plasma kisspeptin and serum reproductive hormones were measured every 15mins for 4hrs. Next, we undertook *rodent studies* in adult C57BL/6J male mice to elucidate the putative mechanism by which intranasally administered kisspeptin can stimulate reproductive hormone release, using intranasal delivery of fluorescently-tagged kisspeptin-54 and a series of c-Fos experiments. Thereafter, we conducted *pharmaceutical studies* to characterise the chemical stability of kisspeptin-54 in solution for nasal delivery in real-time.

Results

Human studies: in healthy men, intranasal kisspeptin rapidly and dose-dependently increased plasma kisspeptin at doses 6.4-25.6 nmol/kg ($P<0.01$ for all doses vs placebo), with peak rises within 15-30 minutes. In parallel, intranasal kisspeptin acutely and robustly increased serum LH at doses 6.4-25.6 nmol/kg ($P<0.01$ for all doses vs placebo) with peak rises at 30 minutes. Similarly, in patients with HA, intranasal kisspeptin acutely increased plasma kisspeptin ($P=0.004$ vs placebo) and serum LH ($P=0.004$ vs placebo). *Animal studies*: To provide mechanistic insight, we demonstrate in male mice that GnRH neurons located in the olfactory bulb express kisspeptin receptors and that intranasal delivery of fluorescently-tagged kisspeptin-54 binds to the olfactory epithelium. *Pharmaceutical studies*: Kisspeptin-54 in 0.9% saline remained within pharmaceutically accepted limits for stability for up to 60 days at 4°C revealing realistic pharmaceutical potential.

Conclusion

We demonstrate robust clinical effects in both healthy volunteers and patients with hypogonadism and provide mechanistic and pharmaceutical evidence for intranasal delivery as a novel, non-invasive and effective kisspeptin administration route for the management of reproductive disorders that would be preferable to patients and clinicians alike and so transform the ongoing development of kisspeptin-based therapeutics.

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OC7.2

BRF1-Mediated Paracrine Signalling by a Subset of SOX2-Expressing Stem Cells is required for Normal Development of the Stem Cell Compartment and Terminal Differentiation of Pituitary Committed Progenitors

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Introduction

Hormone-producing pituitary cell lineages derive from SOX2+ embryonic precursors. These cells maintain multipotency into early postnatal life, acting as the resident population of pituitary stem cells (PSCs) and contributing extensively to all the endocrine cell lineages. Additionally, paracrine signalling from PSCs is important for cell proliferation of neighbouring progenitors (PMC7803373). It is not known if SOX2+ PSCs are involved in the regulation of additional cell attributes during normal physiology, and if there is functional heterogeneity among the SOX2+ PSC population.

Experimental Methods

We have carried out single cell RNA-Sequencing of SOX2+ PSCs from $Sox2^{Egfp/+}$ mouse pituitaries at three postnatal stages from P3 to P56 and used computational approaches to analyse their molecular signatures. A novel conditional mouse model expressing a constitutively active mutant form of the RNA binding factor BRF1 ($R26^{stop\text{-}mBRF1}$) has been used to attenuate the expression of several cytokines and chemokines in SOX2+ cells (PMC4589897).

Results

We show that the SOX2+ PSC population consists of three subgroups (SC1, SC2 and SC3). While SC1-SC2 express abundant cytokines and secreted factors, suggesting paracrine function, SC3 expressing *Lef1*, is identified as a committing PSC cluster. Key markers of PSC clusters SC1-SC2 include the RNA binding factor BRF1. We show that BRF1 is highly expressed in PSCs in both mouse and human pituitaries by IHC. Secondly, we show that the dysregulation of BRF1 in embryonic SOX2+ cells using the *Hesx1-Cre* driver (PMC3461924) results in pituitary hypoplasia and severe hypopituitarism due to a failure of the PIT1 and SF1 cell-lineage committed progenitors to terminally differentiate into hormone-producing cells. Additionally, there is a significant reduction of the stem cell compartment, manifested by lower numbers of SOX2/SOX9+ stem cells. This phenotype is recapitulated when using a *Sox2-CreERT2* driver (PMID24094324). The differentiation failure can be rescued *in vitro* through co-culture of mutant cells with wild-type stem cells, as well as in vivo, in mutant pituitaries where activation of constitutively active BRF1 is restricted to few SOX2+ PSCs in a mosaic manner. Finally, we identify key ligands underlying this differentiation phenotype, and demonstrate a partial restoration of terminal differentiation in the mutant, when cultured in the presence of these ligands.

Conclusion

We provide evidence indicating the presence of functionally distinct groups of SOX2+ pituitary stem cells and reveal a critical role for a PSC subset in the development of the stem cell compartment and in driving terminal differentiation of committed progenitors.

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OC7.3

The mesenchymal stem cells induce immunosuppressive microenvironment in pituitary tumors

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The tumor microenvironment (TME) includes diverse cellular components such as mesenchymal stem cells (MSC) and immune cells. MSC are a subset of heterogeneous cell populations characterized by the expression of CD105, CD73, and CD90 that can differentiate into chondrocytes, osteoblasts, and adipocytes *in vitro*. They are known to have immunomodulatory capabilities. Our aim was to isolate and characterize the immunomodulatory capabilities of MSC from pituitary tumors (PT) and non-tumoral gland as well as to describe the immune TME. We isolated and cultivated MSC from LH/FSH-PT and ACTH-PT, as well as non-tumoral pituitary glands. The MSC obtained from PT and non-tumoral gland were co-cultured in the presence of monocytes from healthy donors and their ability to transform into M0, M1 or M2 macrophages was assessed by flow cytometry. The results showed that pituitary tumors derived MSC induce an immunosuppressive M2 macrophage state, by increasing the expression of CD14 and CD206 markers, and decreasing HLA-DR. Upon co-culturing them with naïve T cells, PT MSC were capable inducing a Treg phenotype. To identify PT TME, we performed tumor whole transcriptome characterization and cellular deconvolution using CIBERSORT. Our analysis was indicative of a strong presence of M2 macrophages, TCD4+ and TCD8+ cells, which was confirmed by immunofluorescence, suggesting an immunosuppressive TME. Thus, the MSC immunosuppressive induction correlates directly with immune TME. ACTH-PT derived MSC showed a stronger anti-inflammatory activity than LH/FSH-PT. We also characterized the transcriptomic differences between non-tumoral and PT derived MSC by means of RNAseq. We found differences between the non-tumoral MSC and pituitary tumor derived MSC, but mainly between ACTH- and LH/FSH-PT derived MSC. In conclusion our data suggest that the presence of MSC influence an immunosuppressive tumor microenvironment alongside with tumor cells.

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OC7.4

Lysine demethylase KDM1A and ectopic expression of GIP-receptor in somatotropinomas of patients with paradoxical response to oral glucose

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Introduction

Paradoxical increase of GH following oral glucose load has been described in ~30% of patients with acromegaly and has been related to the ectopic expression of the glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) in somatotropinomas. Recently, we identified germline pathogenic variants of lysine demethylase 1A (*KDM1A*) in patients with GIP-dependent primary bilateral macronodular adrenal hyperplasia with Cushing's syndrome. Patients also displayed a deletion of chromosome 1p, including the *KDM1A* locus in their adrenal tissues, resulting in complete loss of KDM1A expression. The ectopic expression of GIPR in both adrenal and pituitary lesions suggests a common molecular mechanism. The aim of our study was to search for genetic abnormalities of *KDM1A* in somatotroph pituitary adenomas.

Methods

We collected somatotropinoma specimens from acromegalic patients followed in two tertiary endocrine centers in France and one in Italy. Somatic DNA was studied by targeted exome NGS and array-CGH. *GIPR* and *KDM1A* expression was quantified in the tumors using digital droplet PCR.

Results

We included 186 patients: 108 patients (70.6 %) had a classic pathological GH response after oral glucose load, whereas 45 patients (29.4%) displayed a paradoxical rise of GH concentrations. Patients with a paradoxical response displayed higher IGF-1 levels (360 $\pm$ 111.8% above ULN vs 309.8 $\pm$ 107.3 %, $P=0.0130$) and less invasive and smaller tumors (14.5 $\pm$ 5.58 mm vs 18.5 $\pm$ 8.73 m, $P=0.0066$). We did not identify any *KDM1A* pathogenic variants amongst the 146 somatotropinomas analyzed by targeted-NGS. However, we identified a recurrent 1p deletion encompassing the *KDM1A* locus in 26 tumors. This 1p deletion was more frequently, but not exclusively, found in patients with paradoxical GH response compared to those with classic GH response. This somatic deletion of one *KMD1A* allele was associated with a lower KDM1A expression ($P=4.5e-5$) and a higher GIPR expression ($P=0.0005$).

Discussion

Unlike in GIP-dependent PBMAH, we did not identify *KDM1A* genetic variants in a large cohort of acromegalic patients, independently of their GH response pattern to oral glucose loading. We identified recurrent 1p deletion in some tumors and pituitary adenomas with a loss of one *KDM1A* copy due to chromosome 1p deletion harbored higher levels of *GIPR* transcripts than adenomas diploid for the *KDM1A* locus. If *KDM1A* haploinsufficiency leads to partial transcriptional derepression at the GIPR locus and a paradoxical rise of GH after glucose load warrants further investigations.

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OC7.5

A novel filamin A-binding molecule may significantly enhance SST2 antitumoral actions in GH-secreting PitNET cells

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The main target of pharmacological therapy for growth hormone (GH)-secreting pituitary tumors (GH-PitNET) is the somatostatin receptor type 2 (SST2). However, approximately half of patients treated with octreotide, an SST2 agonist, show a low response rate or are octreotide-resistant. Here we present mechanistic data that shows co-treatment with simufilam, a novel oral therapeutic candidate, enhances sensitivity to octreotide. We previously showed that the cytoskeleton protein filamin A (FLNA) is recruited to bind SST2 upon agonist stimulation, and this interaction is required for SST2 signaling in GH-PitNET cells. However, when phosphorylated at Ser2152, FLNA no longer enables SST2 signaling and all SST2 anti-tumor effects are abolished. Simufilam is a FLNA-binding small molecule shown to modulate FLNA's conformation and its interactions with partner proteins in disease states. We postulated that simufilam may restore FLNA's linkage to SST2 and therefore FLNA's ability to enable SST2 signal transduction. To test this hypothesis, we assessed simufilam's effects on FLNA phosphorylation, FLNA-SST2 complex formation, SST2 signal transduction, GH secretion and cell proliferation/apoptosis, in human primary cultured GH-PitNET cells and in the rat pituitary tumor cell line GH4C1. Simufilam treatment reduced FLNA phosphorylation on Ser2152 in GH4C1 cells (-28$\pm$13% after 10 min, $P<0.01$ vs basal) and in primary human GH-PitNET cells (-59%). Additionally, FLNA-SST2 complexes in GH4C1 cells fell below basal levels after 1h octreotide treatment (-29$\pm$6.8%, $P<0.05$ vs bas) but were still elevated after 1h co-incubation with octreotide + simufilam (135$\pm$19.7%, $P<0.05$ vs bas). Simufilam did not affect the ability of octreotide to inhibit GH secretion in GH4C1 or primary GH-PitNET cells that are *in vitro* responsive to octreotide; however, a combination of simufilam + octreotide reduced GH secretion in primary GH-PitNET cells that are *in vitro* resistant to octreotide ($n=2$) (-42$\pm$3.5%, $P<0.001$ vs bas). Simufilam slightly reduced cell proliferation (-15$\pm$10.1%, $P<0.05$ vs bas) and ERK phosphorylation (-21$\pm$18.8%, $P<0.05$ vs bas), while increasing cell apoptosis (+17.8$\pm$7.3%, $P<0.05$ vs bas) in the GH4C1 cell line. Interestingly, co-treatment with simufilam + octreotide in GH4C1 potentiated the pro-apoptotic effect of the single drugs (+13$\pm$5% octreotide, $P<0.001$ vs bas; +36.8$\pm$9.2% octreotide + simufilam, $P<0.01$ vs bas, $P<0.05$ vs octreotide or simufilam alone). In conclusion, simufilam reduced FLNA phosphorylation, enhanced and prolonged the octreotide-induced FLNA-SST2 interaction and promoted SST2 signal transduction in human primary cultured GH-PitNET cells. These data suggest that co-treatment with simufilam may enhance the efficacy of octreotide or other somatostatin analog drugs in the management of pituitary tumors.

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OC7.6

Pathophysiological role of splicing machinery in craniopharyngiomas: Novel source of diagnostic, prognostic and therapeutic biomarkers

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Craniopharyngiomas (CPs) are a relatively benign subtype of epithelial tumors that typically originate from the sellar and suprasellar regions of the brain. These endocrine tumors are classified as adamantinomatous (ACP) or papillary (PCP)

based on their histological characteristics. Unfortunately, the diagnosis of CPs is frequently made at an advanced stage of tumor development, and therefore relevant associated comorbidities are often present. The first-line treatment is typically surgical intervention; however, complete resection is often not achieved leading to high rates of recurrence. Therefore, there is an urgent need to identify alternative diagnostic, prognostic, and therapeutic tools to improve the management of CPs. Recently, growing evidence indicates that RNA splicing-process is altered in different endocrine-related tumors which leads to the generation of altered spliceosome components (SCs), splicing factors (SFs), and/or aberrant splicing-variants (SVs) associated with cancer progression, aggressiveness and development. Therefore, our aim was to explore the putative oncogenic role of key splicing-related factors in CPs through: 1) interrogating the expression profile of key splicing machinery components in ACP ($n=36$) and PCP ($n=4$) vs control samples [$n=11$; normal-pituitaries (NP)]; and 2) implementing different bioinformatic and functional approaches (RNAseq and CP primary cell-cultures). Our results revealed a substantial number of SCs and SFs are drastically altered in ACP vs NP, and also when primary vs recurrent ACP were compared. Specifically, 4 SFs were identified as the most discriminating diagnostic/prognostic factors, being corroborated in additional human cohorts. These SFs were also associated with key clinical parameters suggesting a potential oncogenic role in CPs. Moreover, dysregulation of 2 of these SFs was also corroborated in RNAseq of an additional cohort of 18 ACP vs 3 NP. *In vitro* overexpression of these SFs in primary ACP-derived cells revealed a critical functional role of these SFs in ACP. In fact, the *in vitro* overexpression induced the phosphorylation of MAPK and AKT pathways and reduced the phosphorylation JAK/STAT, NF-kB and TGFB which might be associated with CP tumorigenesis. Finally, relevant SVs that are associated to CP development and progression (e.g., *GNAS*) were identified as potential oncogenic linkers with the observed splicing-machinery dysregulation. In conclusion, spliceosome is drastically altered in CPs, wherein some SFs could represent attractive novel diagnostic/prognostic and therapeutic targets for this endocrine pathology.

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Oral Communications 8: Calcium and Bone

OC8.1

Clinical picture of early infancy PTH-resistance syndromes: is it time to improve diagnostic criteria?

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Since the first description of inactivating PTH/PTHrP signaling disorders (iPPSDs, historically named pseudohypoparathyroidism (PHP)) a remarkable clinical variability was observed, especially in clinical presentation, which seems to be age-dependent. The main clinical features, including PTH resistance, brachydactyly and short stature, develop during mid and late childhood, whilst minor clinical features such as a round face, rapid weight gain and subclinical hypothyroidism are the most prevalent signs in toddlers, e.g., age <2 years. The latter are included among minor criteria for diagnosis and present a large overlap with other conditions, therefore a significant delay in diagnosis has been reported. The aim of our study was to analyse a large cohort of iPPSD patients and to describe early natural history of the disease, to improve the diagnosis and reduce the diagnostic delay, through the development of new diagnostic criteria for early infancy. We collected data from 117 patients diagnosed with iPPSDs regularly followed-up at the Endocrinology Unit of two European tertiary centres. We retrospectively collected data on the age of onset of main clinical and hormonal features. In our cohort the mean age at diagnosis was 7.2 ± 6.7 years old. The onset of PTH resistance and brachydactyly, major criteria for diagnosis, was significantly different from that of both TSH resistance and obesity (median age 6.1, 5.8, 1.85 and 2 years old, respectively). In contrast, no statistically significant difference was detected between the age onset of PTH resistance and brachydactyly and the age onset of TSH resistance and obesity. We can therefore speculate that these two pairs of symptoms are tightly age-related. As for diagnostic criteria, we studied the distribution of both major and minor criteria in patients before 2 years. Minor criteria were more represented than major criteria in this population ($P=0.002$). Indeed, in 64% of patients before 2 years none of the major criteria was described, conversely 71% of these population had already developed at least 1 minor criteria. In details, 20% of patients had developed TSH resistance and obesity before 2 years, while only 2% of patients had developed PTH resistance, brachydactyly and ectopic ossifications before 2 years. In conclusion, the clinical picture of iPPSDs in early infancy differs from that of adults, thus current diagnostic criteria may not be appropriate for children. In detail, the combination of early onset obesity and elevated TSH levels, currently included among minor criteria, should trigger the genetic screening in infants before 2 years old.

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OC8.2

Eneboparatide, a Novel PTH-1 Receptor Agonist, Has No Impact on Bone Parameters Following Chronic Treatment of Non-Human Primates

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Eneboparatide (AZP-3601) is a novel, synthetic, 36-amino-acid peptide agonist of the parathyroid hormone type 1 receptor (PTHR1), with potent selectivity for the R0 conformation. This results in prolonged calcemic responses, while having a short circulating half-life. Eneboparatide is being developed for the treatment of chronic hypoparathyroidism (cHP). Studies in hypoparathyroid animal models and, most recently, in hypoparathyroid patients, have demonstrated that eneboparatide is effective in maintaining normal serum calcium in the absence of calcium/vitamin D supplementation and in normalizing urinary calcium excretion without deleterious impact on bone parameters. To further examine the effect of chronic eneboparatide treatment on bone, both 13-week and 39-week studies were conducted in non-human primates (NHP), which are considered a relevant species with regard to eneboparatide effects on serum calcium. Groups of 3 or 4 Cynomolgus monkeys of each sex were given daily subcutaneous injections of either vehicle or eneboparatide at doses of 1, 2.5 or 10 µg/kg for either 13 or 39 weeks. At the end of the 13-week study, right femur, right tibia and the L4 lumbar vertebra were collected from 3 animals/group/sex and bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry. The left femur was submitted to histopathological examination. There was no evidence of any treatment-related effect on either BMD or histopathology. In the 39-week study, blood samples were collected from 4 animals/group/sex prior to and during weeks 4, 8, 13, 26 and 39 of treatment for measurement of bone biomarkers. In-life BMD of left femur, left tibia and L4 lumbar vertebra was measured by quantitative computed tomography prior to and during weeks 26 and 39 of treatment. At the end of the treatment period, femurs were processed for histopathological examination. Analysis of blood samples for the anabolic bone biomarker, N-terminal propeptide of type 1 procollagen (P1NP), and the catabolic bone biomarker, C-terminal telopeptide (CTX), revealed no treatment-related changes at any time in either sex. Prior to treatment, BMD was homogeneous among all groups for all the three bone sites examined. Over the course of the study, there were no statistically significant changes in BMD as compared to pre-treatment values, regardless of sex or eneboparatide treatment. Subsequent histological examination of the femur revealed no noteworthy findings. These results, demonstrating an absence of deleterious effect of chronic eneboparatide treatment on bone in NHP, further substantiate the potential of eneboparatide as an ideal treatment for hypoparathyroidism.

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OC8.3

The thiazide challenge test to differentiate between primary hyperparathyroidism and secondary hyperparathyroidism due to idiopathic hypercalciuria.

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Background
Treatment of primary hyperparathyroidism (PHPT) and secondary hyperparathyroidism due to idiopathic hypercalciuria (SHPT-IH) is markedly different. Nevertheless, differentiating one from another remains a challenge and robust diagnostic tools are lacking. The thiazide challenge test (TCT) has been proposed

as a means to aid clinicians in their decision making. However, evidence supporting its use is scarce.
Materials and Methods
We performed a retrospective analysis of 25 patients who underwent a TCT at the Ghent University Hospital (Belgium). We assessed serum and urinary samples before and after testing, clinical and imaging outcomes as well as therapy and long-term follow-up to evaluate the efficacy of the TCT. Based on literature and the calcium load test, other potentially useful parameters were calculated.
Results
Baseline serum albumin-adjusted calcium (AACa) and serum total calcium (TCa) were not significantly different between patients with PHPT and SHPT-IH (2.54 (±0.072) vs 2.55 mmol/l (±0.13) and 2.63 (±0.069) vs 2.64 mmol/l (±0.15) respectively). During the TCT, AACa rose 0.11 mmol/l (±0.10) in patients with PHPT and 0.0071 mmol/l (±0.10) in patients with SHPT-IH. The change in AACa is significantly different between both groups (one-sided $P=0.025$). A similar result was found for TCa, which rose 0.14 mmol/l (±0.12) in patients with PHPT compared to 0.012 mmol/l (±0.15) in patients with SHPT-IH (one-sided $P=0.024$). The TCT can detect PHPT based on an increment in AACa of at least 0.10 mmol/l or in TCa of at least 0.13 mmol/l with a calculated sensitivity of 81.8% and a specificity of 77.8%. Serum parathormone (PTH) levels and urinary calcium excretion (UCE) did not differ between patients with PHPT and SHPT-IH (101.7 ng/l (±26.9) vs 105.7 ng/l (±53.8) and 10.9 mmol/24 hours (±3.0) vs 9.4 mmol/24 hours (±3.2) respectively). PTH levels, UCE, the calcium-phosphorous ratio (Ca/P), the PTH-inhibition rate (PTH-IR) and the parathyroid function index (PF-index) did not differ significantly between patients with PHPT and SHPT-IH during the TCT.
Conclusion
The TCT can aid in discriminating patients with PHPT from those with SHPT-IH based on the rise in serum calcium. It can be easily used in all patients with nephrolithiasis or hypercalciuria, an elevated PTH, and a normal to slightly elevated serum calcium. Even though mild hypokalemia occurs frequently, and caution is warranted, no severe side effects were observed. Other variables such as serum PTH, UCE, Ca/P, PTH-IR and PF-index did not differentiate between both groups. Larger prospective trials are necessary to reassess the relevance of different biochemical parameters and the diagnostic potential of the TCT.

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OC8.4

Bone mineral density and fracture status of differentiated thyroid cancer patients under TSH suppression treatment

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Aim
Thyroid Stimulating Hormone (TSH) suppression treatment may have a detrimental effect on bone tissue in differentiated thyroid cancer (DTC) patients. The current study aimed to investigate vertebral fracture, bone mineral density measurements, and TSH levels in DTC patients under levothyroxine (LT4) suppression treatment after total thyroidectomy and/or radioiodine ablation therapy in a multicentric setting.
Material and Method
This multicentric cross-sectional study was conducted at 21 medical centers from 12 cities in Turkey. Clinical data, serum TSH, free thyroxine (FT4), Thyroglobulin (Tg), and antithyroglobulin (Anti-Tg) levels were all recorded during the most recent visit. TSH serum concentrations were classified as TSH < 0.1 mU/l, TSH 0.1-0.5 mU/l and TSH > 0.5 mU/l according to TSH suppression recommendation of American Thyroid Association guidelines. Systolic and diastolic blood pressure and pulse rate were measured. Mineral densities were measured with a GE Lunar DXA scanner. Lateral vertebral X-rays were reviewed blindly. The vertebral fractures were defined according to Genant's semi-quantitative method as grade 1-4.
Results
A group of 990 DTC patients (F/M:829/161,51.4±11.5 years) were enrolled. The mean disease duration was 5.2±4.4 years. LT4 daily dosage was 131.1±37.5 mg/day. The patient's femur neck BMD ($P=0.65$) and L1-L4 BMD ($P=0.86$) levels were similar according to TSH suppression levels. Serum calcium, phosphor, parathormone, and 25-OHD3 levels were similar between groups. Four hundred sixty-eight lateral vertebral x-ray evaluations revealed that 200 patients had fractures. Mean vertebral fracture number was 5.43. The patients with vertebral fractures were older ($P<0.001$), The daily dosage ($P<0.001$) and dose per kg ($P=0.015$) were lower in the fracture group compared to the nonfracture group. The fracture group's femur neck BMD ($P=0.001$) and L1-L4 BMD ($P=0.003$) were lower. The TSH levels of the patients with fractures were higher ($P=0.0082$).
Conclusion
The femur and L1-L4 BMD levels of patients in this study group were similar according to TSH suppression levels. Studies to date have also yielded conflicting results. Frequent monitoring and avoiding unnecessary TSH suppression especially in older patients is essential to prevent detrimental effects.

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OC8.5

A vitamin D receptor antagonist as a potent and safe treatment for Idiopathic Infantile Hypercalcemia

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Idiopathic Infantile Hypercalcemia (IIH) is a rare inborn form of severe vitamin D hypersensitivity, with an estimated incidence of 1:33.000 live birth and a high degree of misdiagnosis. Since the identification of CYP24A1 loss-of-function variants inducing IIH in 2011, over 41 pathogenic variants have been described, and represent the major genetic drivers of IIH[1]. CYP24A1 encodes the main catalytic hydroxylase of the bioactive form of vitamin D (1,25D3). Upon binding to its nuclear receptor VDR, 1,25D3 regulates intestinal calcium absorption, renal calcium reabsorption and bone resorption, thus playing a key role in calcium homeostasis. IIH phenotype embraces a wide range of clinical features and the current therapeutic protocols, aimed to control long-lasting and recurrent hypercalcemic episodes, do not selectively target vitamin D signalling. In addition, long-term and high-dose regimens negatively impact patient's quality of life, and a protracted administration is not always advisable. Thus, there is a significant unmet medical need for selective treatments for this metabolic disorder. We have shown that the VDR antagonist ZK168281 (ZK) normalizes VDR signaling and prevents 1.25D3-induced hypercalcemia in wild type mice, without any obvious side effect[2]. To determine the therapeutic potency of ZK for IIH, we generated CYP24A1-null mice and showed that they recapitulate the human disease, including biochemical changes in mineral metabolism (e.g. hypercalcemia, hypercalciuria), renal abnormalities (e.g. nephrolithiasis, tubular fibrosis and glomerular injury), suppressed levels of parathyroid hormone and bone mineralization defects. Moreover, we demonstrated that serum calcium

levels and renal calcium excretion fall back within physiological ranges in Cyp24a1-null mice treated for 2 weeks with ZK. In addition, we showed that this treatment improves nephrocalcinosis and renal fibrosis of Cyp24a1-null mice, highlighting the therapeutic potency of ZK. As little is known about the tissue-specific molecular events secondary to hypercalcemia induced by CYP24A1-deficiency, we performed a comparative genome-wide transcriptomic analysis in the key vitamin D target tissues, namely intestine, kidney and bone. In depth bio-informatic analysis revealed the key pathways involved in the disease, and importantly, we demonstrated that ZK normalizes these transcriptomic alterations of Cyp24a1-null mice. Thus, this compound, that selectively targets VDR, represents a potent and safe therapeutic option and opens new avenue for the treatment of refractory rare diseases secondary to hypervitaminosis-D.

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OC8.6

Skeletal phenotypes in postmenopausal women with primary hyperparathyroidism (PHPT)

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Current clinical presentation of PHPT is mild disease with an increased risk of fragility fractures. PHPT predominantly occurs in postmenopausal women, who have an increased risk of osteoporosis and fractures due to ageing and loss of estrogen.

Aims

To explore skeletal phenotypes in postmenopausal women affected by PHPT with a wide clinical and biochemical spectrum of disease.

Patients

Postmenopausal (at least 5 years from last menses) women with PHPT were retrospectively evaluated at three third level Italian centers for management of osteoporosis and mineral metabolism disorders ($n=120$ from Milan, $n=134$ from Cuneo, $n=132$ from Pisa).

Methods

Data were collected from clinical records and analyzed by nonparametric Spearman correlation and multiple linear regression. Hierarchical clusterization by Wards' method and Euclidean similarity index identified skeletal phenotype clusters; differences among clusters were detected by Kruskall-Wallis ANOVA.

Results

Considering the whole 386 PHPT women [aged 68.0 (61.0-74.0) years], fractures (clinical and morphometric vertebral, femur, humerus, pelvic, wrist fractures) positively correlated with phosphatemia and negatively with lumbar and neck T-scores. Cluster analysis based on fractures number, phosphatemia, lumbar and neck T-scores, identified 4 clusters: the most frequent phenotype ($n=307$) included women with lumbar osteoporosis and neck osteopenia with a prevalence of fractures of 29.5% (0-3 fractures, minimum-maximum) and higher 24-hours urinary calcium corrected for body weight (UCa). The second phenotype included women ($n=16$) with more important lumbar and neck osteoporosis who all experienced multiple (3-6) fractures. The third phenotype included women ($n=37$) with neck osteopenia/osteoporosis and mild lumbar osteopenia with a prevalence of fractures of 23.3% associated with lower UCa and estimated glomerular filtration rate (eGFR). The forth phenotype included women ($n=19$) with lumbar and neck osteopenia with a very low prevalence of fractures (2.1%, no more than 1 fracture). In this cluster, women were younger and heavier, with lower PTH levels. Unexpectedly, ionized and total calcium, phosphate, bone and total alkaline phosphatase, 25hydroxyvitamin D (25OHD) levels, and kidney stones prevalence (ranging 21.1-30.2%) were similar among the 4 clusters. Fractures were predicted by lumbar T-score. Besides, lumbar T-score was predicted by body mass index, 25OHD, eGFR and neck T-score.

Conclusions

Skeletal involvement in this large retrospective series of postmenopausal women with PHPT presented with heterogeneous phenotypes associated with different prevalence of fractures. Fractures were related with bone mineral density, but not with PHPT severity, suggesting that other factors besides PHPT should be considered in the evaluation of the bone involvement in postmenopausal women with PHPT.

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Oral Communications 9: Adrenal and Cardiovascular Endocrinology 2

OC9.1

Identification of adrenocortical masses malignancy and aggressivity through radiomics: a pilot study

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Background

Adrenal lipid poor adenoma (LPA) and adrenocortical cancer (ACC) may overlap in computerized tomography (CT). Radiomics recently emerged as new tool for malignant behavior identification.

Aim

To assess radiomics utility for identification of ACC and LPA in adrenocortical masses with unenhanced (UE) CT scan attenuation ≥ 10 Hounsfield Unit (HU).

Methods

We retrospectively enrolled 50 patients, 38 radiologically defined LPA with 6-12 months of radiologic stability or benign histological exam ($n=11$), and 12 ACC with histological exam (2 patients with Weiss score $=3$; 4 patient with ki67 $\geq 10\%$). All patients underwent CT with UE scan, arterial (ACE), venous (VCE) and 15' delayed (DCE) contrast enhanced phases, on which radiomics was performed with LIFEx software (©LITO 2022-2023). We performed a two-steps multivariate analysis for each CT phase to evaluate predictors of malignancy (Weiss score ≥ 3). Multivariate analysis first step was completed within single radiomics feature classes, then first step predictors were altogether employed for multivariate analysis second step. Second step predictors were utilized for receiver operating characteristic curve analysis and estimation of positive (PPV) and negative predictive value (NPV). We conducted multivariate analysis for each CT phase, within single radiomics feature classes, to evaluate predictors of ki67 values, as aggressivity marker.

Results

In UE, surface to volume ratio (SVR) and Run Length Non-Uniformity (RLNU) predicted malignancy (Odds Ratio (OR) $=2.718$; 95% Confidence Interval (CI) $=$ 1.56-4.75; $P<0.001$), with 83.3% sensibility, 94.3% specificity, 83.3% PPV, 94.7% NPV. Model including HU total lesion glycolysis (TLG), standard deviation, variation coefficient and maximum gray level predicted ki67 ($R^2=$ 0.984; $P<0.001$). In ACE, SVR and Feret diameter predicted malignancy [OR $=$ 2.718; 95% CI $=1.57$-4.745; $P<0.001$], with 83.3% sensibility, 92.1% specificity, 76.9% PPV, 94.6% NPV. Model including HU TLG, energy, variation coefficient and total calcium score predicted ki67 ($R^2=0.998$; $P<0.001$). In VCE, SVR and compacity predicted malignancy [OR $=2.719$; 95% CI $=1.54$-4.79; $P<0.001$], with 83.3% sensibility, 92.1% specificity, 76.9% PPV, 94.5% NPV. Model including HU maximum histogram gradient, root mean square and intensity histogram minimum grey level predicted ki67 ($R^2=0.979$; $P<0.001$). In DCE, SVR and RLNU predicted malignancy [OR $=2.718$; 95% CI $=1.54$-4.79; $P<0.001$], with 83.3% sensibility, 91.9% specificity, 76.9% PPV, 94.5% NPV. Model including HU TLG and median absolute deviation predicted ki67 ($R^2=0.98$; $P<0.001$).

Conclusion

Radiomics seems useful to identify adrenal masses nature, even without CT contrast enhanced phases. Among other radiomics parameters, SVR and HU intensity-based features seem to be powerful predictors of adrenocortical masses malignancy and aggressivity.

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OC9.2

FLNA-binding partner Wee1 as a new potential pharmacological target in adrenocortical carcinomas

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The cytoskeletal actin-binding protein filamin A (FLNA) is poorly expressed in adrenocortical carcinomas (ACC) compared to adenomas (ACA), and this might contribute to sustain the increased cell proliferation by downregulating IGF1R expression and its downstream signaling. In mouse neural progenitor cells, increased protein expression levels of the CDK1 kinase Wee1 have been found after loss of FLNA. This protein has a leading role in regulating the G2-M checkpoint and functions as a mitotic inhibitor. Wee1 is overexpressed in several cancer types and its pharmacological inhibitor Adavosertib (AZD1775) is currently undergoing clinical trials. Aims of the present project are to investigate the role of FLNA in regulating Wee1, the effects of Wee1 inhibition on cell proliferation and apoptosis, as well as the effects of FLNA levels on AZD efficacy in human H295R and MUC-1 cell lines. The analysis of protein expression levels of FLNA and Wee1 in 6 ACC and 8 normal adrenal tissues revealed that ACC express lower levels of FLNA (0.4 ± 0.7 and 2.9 ± 0.9, respectively, $P<0.05$), while significantly increased Wee1 (0.26 ± 0.1 and 0.01 ± 0.06, respectively, $P<0.001$). In MUC-1 cells a correlation between Wee1 and FLNA expression was shown. Indeed, FLNA silencing induced an increased expression of Wee1, phosphorylated CDK1 and cyclin B1 ($+1.6\pm0.2$, $+1.7\pm0.4$ and $+1.4\pm0.2$ fold, $P<0.001$ vs negative control, respectively). On the contrary, FLNA overexpression resulted into a reduced expression of Wee1, phosphorylated CDK1 and cyclin B1 (-$51\pm5\%$, $P<0.001$, $-60\pm5\%$, $P<0.001$, $-67\pm20\%$, $P<0.01$ vs mock). Treatment with AZD1775 induced a dose-dependent reduction of cell proliferation (-$32\pm4.6\%$, $P<0.001$; $-78\pm4.8\%$, $P<0.001$ vs bas at 250 nM) and an increase of apoptosis ($+6\pm1.5$-fold, $P<0.001$; $+4\pm0.5$-fold, $P<0.001$ vs bas at 1 μM) in H295R and MUC-1 cell lines, respectively. Flow cytometric analysis of apoptotic subpopulations showed that, in MUC-1, Wee1 inhibition specifically stimulated an increase of the early apoptotic cells ($+5$-fold, $P<0.001$ vs bas at 1 μM). Moreover, AZD1775 induced a time-dependent reduction of CDK1 phosphorylation, with a maximum after 2 hours (-$67\pm9.5\%$, $P<0.01$; $-90.5\pm1.7\%$, $P<0.001$ vs bas at 250 nM in H295R and MUC-1, respectively). Interestingly, FLNA knockdown potentiated AZD1775 effects on cell proliferation (-$51\pm6.4\%$, $P<0.01$ vs negative control at 250 nM) in MUC-1 cells. In conclusion, this work demonstrates that low FLNA levels in ACC correlate to a high Wee1 expression, contributing to an increased cell growth. Moreover, it proposes Wee1 inhibition as a new potential therapeutic approach for ACC, particularly for those lacking FLNA.

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OC9.3

Prolonged exposure to target mitotane concentrations is associated with better recurrence-free survival in patients with adrenocortical carcinoma on adjuvant treatment

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Background
The management of adjuvant mitotane therapy in patients with adrenocortical carcinoma (ACC) is challenging. Plasma mitotane concentrations > 14 mg/l have been associated with efficacy in the treatment of advanced ACC; however, data in the adjuvant setting are mixed. Moreover, there is no consensus on how to assess the optimal exposure to mitotane and all the proposed methods have inherent limitations. We have recently proposed a new method analogous to what is established for the anticoagulant warfarin, the time in target range (TTR). We aimed to evaluate whether the TTR is a factor influencing recurrence-free survival (RFS) in patients with ACC on adjuvant mitotane.
Methods
This is an international, retrospective, cohort study undertaken in 18 centers in 8 countries, under the auspices of the European Network for the Study of Adrenal Tumors (ENSAT), including adult patients with ACC who were treated with adjuvant mitotane for at least 1 year following tumor resection, with the availability of at least 3 mitotane measurements per year. TTR was calculated with the Rosendaal method and expressed as the number of months with plasma mitotane concentration > 14 mg/l. The following potential predictive factors for RFS have been investigated: patient sex and age, ENSAT stage, hormone secretion, resection status, Weiss score, Ki67 index, and TTR. Data are expressed as median and interquartile range.
Results
From a total of 254 patients, 157 fulfilled inclusion criteria and were analyzed (F/M 94/63; age 49, 41-58 years), with a follow-up of 49 (33-92) months. The key baseline features were: 7.0% stage I, 69.4% II, 22.3% III, 1.3% IV; 51.6% secreting tumors; 87.2% R0, 2.6% R1, 10.2% RX; Weiss score 5 (4-7); Ki67 index 11 (5-20). All patients initiated mitotane within 3 months from surgery and were treated for 25 (22-36) months, with a TTR of 14 (6-21) months. At multivariate analysis, Ki67 index (HR 1.07, 95% CI, 1.02-1.12; $P<0.01$) and Weiss score (HR 1.7, 95% CI, 1.16-2.47; $P<0.01$) were associated with an increased risk of recurrence, while female sex (HR 0.14, 95% CI, 0.04-0.58; $P<0.01$) and TTR (HR 0.80, 95% CI, 0.70-0.90; $P<0.001$) were associated with a reduced risk.
Conclusions
The present findings show that the patients who are exposed to plasma mitotane > 14 mg/l for longer periods have better RFS. These findings provide indirect evidence of the value of adjuvant therapy with mitotane and support the importance of drug monitoring and dose adjustment in clinical practice to improve treatment response.

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OC9.4

Recovery of adrenal function after stopping mitotane in patients with adrenocortical carcinoma

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Background
Mitotane is regularly used in patients with adrenocortical carcinoma (ACC) adjuvantly, in patients with high risk of recurrence, and in advanced disease. Multiple effects of mitotane result in adrenal insufficiency in virtually all patients. However, it is unclear how frequently the hypothalamic-pituitary-adrenal (HPA) axis is recovering after treatment discontinuation. Here, we aim to investigate the HPA axis after treatment with mitotane.
Methods
We screened patients with ACC treated with mitotane for ≥12 months since 2000 and discontinued treatment without evidence for disease. Minimum follow-up after mitotane discontinuation was 1 year. Data on patients and tumor characteristics, mitotane treatment, and information on HPA axis were analyzed. Primary endpoint was time to adrenal recovery. Explorative analysis of predictive factors (e.g. sex, age, follow-up in reference center, cumulative mitotane dose and plasma levels, duration of treatment, and dose of hydrocortisone-equivalent replacement) was performed using univariate and multivariate Cox regression.
Results
56 patients (36 women) treated with mitotane alone ($n=47$) or in combination with radiotherapy ($n=3$) or chemotherapy ($n=6$) were included. Median duration of mitotane treatment was 25 (14-122) months, with a median average daily dose of 2.8 g (0.70-10.10). The average daily dose of hydrocortisone-equivalent replacement during mitotane treatment was in median 49.4 mg (25.7-66.9). Complete adrenal recovery was documented after a median of 26 (95% CI 19.6-32.4) months in 32 (57.1%) patients. Among these, 22 (68.7%) achieved HPA recovery within 24 months. However, when patients were followed in reference centers ($n=38$), a significantly larger proportion of cases (71.1%) achieved HPA recovery (HR=4.65, 95%CI=1.76-12.25, $P=0.002$). Partial and insufficient recovery were observed in 9 (16.1%) and 15 (26.8%) patients, respectively. In 4 patients (7.1%) with a follow-up>60 months, a long-term adrenal insufficiency has to be assumed. A maximum mitotane peak ≥27 mg/l as well as plasma levels ≥12 mg/l at discontinuation correlated with significant longer time to adrenal recovery (HR=0.24, 95% CI=0.07-0.85, $P=0.03$, and HR=0.45, 95% CI=0.21-0.95, $P=0.03$, respectively). A higher mitotane exposure, as assessed by the area under the curve of mitotane plasma levels, was slightly associated with longer adrenal recovery (HR=0.5, 95% CI=0.2-1.0, $P=0.06$). At multivariate analysis, only plasma levels ≥12 mg/l at discontinuation slightly correlated with longer time to HPA recovery (HR=0.47, 95% CI=0.21-1.06, $P=0.07$).
Conclusions
Our study demonstrates that adrenal recovery occurs in most patients treated with mitotane. Testing for adrenal insufficiency is performed more often in reference centers. Therefore, a sufficient patient follow-up including education on glucocorticoid reduction is needed after mitotane discontinuation.

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OC9.5

Generation of novel tools for the study and development of targeted therapeutic approaches for pheochromocytoma and paraganglioma

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Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumours, which arise from neural crest (NC)-derived structures: the adrenal medulla and the paraganglia. Around one third of PPGLs are associated with inherited cancer susceptibility genes, the highest rate among all tumour types. Currently, the only diagnostic criterion for malignant disease is the presence of metastasis and no molecular or histological features have been identified that help predict risk. Additionally, understanding the pathogenesis of PPGLs and development of new therapies is hindered by the lack of validated disease models. In many tumours, cancer cells with stem-like properties are at the root of tumour initiation/maintenance due to their ability to self-renew and proliferate, but a stem cell population of the adrenal medulla has not been identified. We show that SOX2, a well-characterised marker of multiple stem cell populations, is expressed in a subset of uncommitted Schwann-cell precursors, which generate chromaffin cells and sympathetic neurons and that SOX2 expression persists postnatally and in adulthood in adrenomedullary sustentacular cells. Using the inducible Sox2-CreERT2 driver, *in vivo* lineage tracing in neonates and adults demonstrates that murine neural crest-derived SOX2+ cells expand to self-renew and give rise to new chromaffin, supporting their function as a novel progenitor/stem cell population. This population is therefore ideal to target for expression of tumour-inducing mutations, to generate transgenic models of PPGLs. We establish a system to isolate and culture pure murine and human populations of adrenomedullary SOX2+ stem cells *in vitro* and demonstrate that these cells can be expanded and gene-edited, to express mutant forms of Succinate Dehydrogenase subunits (SDHx), responsible for most hereditary PPGL cases. Finally, normal and mutated SOX2+ adrenomedullary stem cells can be implanted *in vivo* onto the chick chorioallantoic membrane (CAM), where they can be assayed for expansion, contribution of chromaffin cells and tumourigenic properties including invasion and metastasis.

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OC9.6

Previous use of anabolic androgenic steroids is associated with persistent impaired myocardial microcirulation

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Background and Aim
Ongoing anabolic androgenic steroids (AAS) use has been linked with left ventricle dysfunction, while information on the effects years after discontinuation is limited. Furthermore, the underlying mechanism behind the impaired cardiac function is unknown. Early signs of cardiomyopathy, such as microvascular dysfunction with global or regional reduced myocardial perfusion can be measured noninvasively by cardiac positron emission tomography (PET) with Rubidium-82 (Rb-82). The aim of this study was to assess myocardial flow reserve (MFR) by PET/CT Rb-82 in current and previous AAS users compared with healthy never user control participants.
Methods
Community-based cross-sectional study including men involved in recreational training. A standard cardiac PET/CT Rb-82 was performed at rest and after adenosine stress-induced. History of AAS use was obtained using a standardized questionnaire. A MFR<2.5 was used as a validated definition of impaired in men without obstructive coronary artery disease.
Results
We included 28 current and 22 former AAS users and 14 recreational athletes with no prior AAS use. The mean (SD) age was 33 (9) years. Accumulated duration of AAS use, geometric mean (95 CI%) was 184 (108; 312) weeks among current users and 99 (52; 187) weeks among former users ($P=0.126$). Duration since AAS cessation, geometric mean (95 CI%) was 17 months (10; 28,) and 13 (59%) former users discontinuated AAS more than one year prior to inclusion. Analyzed as continuous variable, both former and current users exhibited lower mean (SD) MFR, 3.1 (0.9) ($P=0.028$) and 3.3 (1.2) vs 4.1 (0.9) ($P=0.046$) as compared with controls of never users. The prevalence of impaired MFR (<2.5) was increased in former and current AAS users compared with controls, 36% and 25% vs 7%, trend test ($P=0.026$). Among previous users, every doubling of accumulated AAS duration was associated with an increased risk of impaired MFR age-adjusted OR of 2.9 [1.05; 810] ($P=0.039$).
Conclusions
Previous and current users of AAS exhibited impaired MFR, suggesting persistent impaired cardiac microcirculatory function.

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Oral Communications 10: Diabetes, Obesity, Metabolism and Nutrition 2

OC10.1

CRTC2 activates the epithelial-mesenchymal transition of diabetic kidney disease through the CREB-Smad2/3 pathway

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Background

Epithelial-mesenchymal transition (EMT) plays a key role in tubulointerstitial fibrosis, which is a hallmark of diabetic kidney disease (DKD). Our previous studies have shown that CRTC2 can regulate glucose metabolism and lipid metabolism at the same time. However, it is still unclear whether CRTC2 participates in the EMT process of DKD.

Methods

We used protein-protein network (PPI) analysis to determine differentially expressed genes in DKD and EMT. Then we constructed STZ plus high-fat diabetic mice model and used HK-2 cells that have been verified to confirm the bioinformatics research results. The efects of CRTC2 on epithelial-mesenchymal transition of diabetic kidney disease through the CREB-Smad2/3 signaling pathway were investigated *in vivo* and *in vitro* using Q-PCR, WB, IHC and double luciferase reporter gene experiments.

Results

Firstly, bioinformatics research showed that CRTC2 may promote the EMT process of diabetic renal tubules through the CREB-Smad2/3 signaling pathway. Furthermore, Western blot results showed that overexpressed CRTC2 could reduce the expression of E-cadherin. CRTC2 and α-SMA were increased in STZ mice. Luciferase activity of α-SMA, the key protein of EMT, was sharply increased in response to overexpressed CRTC2 and decreased by silencing in CREB and Smad2/3. In the Q-PCR experiment, the mRNA of α-SMA increased significantly when CRTC2 was overexpressed and decreased partly when CREB and Smad2/3 were silenced. However, E-cadherin had the opposite result.

Conclusion

This study demonstrated that CRTC2 activates the EMT process via the CREB-Smad2/3 signaling pathway in diabetic renal tubules.

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OC10.2

Characterization of the insulinotropic and glucose lowering actions of hybridized amphibian host defence peptide, tigerinin-1R

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Aim

Our previous studies indicated the potential antidiabetic actions of the amphibian host-defence peptide, tigerinin-1. Tigerinin-1R was conjugated with gastric inhibitory polypeptide (GIP) as part of strategies for further development of its therapeutic effects. This study characterises the insulin-releasing and cytotoxic properties of the resulting hybrid peptide.Method: Pure G-TGN was commercially synthesized G-TGN. Insulin releasing effects were assessed using BRIN-BD11 cells incubated with graded concentrations (0 – 3 μM) of the peptide. Cytotoxicity and effect of G-TGN on cell viability were assessed by LDH and MTT assays respectively. Actions of G-TGN on erythrocyte haemolysis, in the presence of increasing glucose concentration, on intracellular calcium level and membrane depolarisation, and on glucose tolerance in diet-induced diabetic mice were investigated.

Results

G-TGN stimulated non-toxic insulin secretion at concentrations ≥ 10 nM ($P<0.05$ to $P<0.001$). At 3 μM, G-TGN was more potent than native tigerinin-1R (1.5-fold, $P<0.01$) and GIP (1.3-fold, $P<0.05$). G-TGN did not affect cell viability nor cause erythrocyte lysis. Insulin-releasing effect of G-TGN was glucose dependent (1.1 mM to 5.6 mM, 1.3-fold, $P<0.05$ and 5.6 mM to 16.7 mM, 1.7-fold, $P<0.01$) and increase in incubations containing KCl (30 mM, 3.6-fold, $P<0.001$) and tolbutamide (200 μM, 2.4-fold, $P<0.01$). Verapamil (50 nM, 23%, $P<0.05$), diazoxide (300 μM, 27%, $P<0.05$) and absence of calcium (19%, $P<0.05$) reduced the effects of G-TGN. G-TGN enhanced intracellular calcium (23%, $P<0.01$) and increased membrane depolarisation (19%, $P<0.05$), and improved glucose tolerance *in vivo* (versus tigerinin-1R, 19%, $P<0.05$; versus GIP, 13%, $P<0.05$).

Conclusion

Hybridization of tigerinin-1R with GIP enhanced its potential and encourages further development of its therapeutic potentials.

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OC10.3

The role of logic learning machine in predicting lipid goal attainment among type 2 diabetes outpatients: Results from the AMD annals study group

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Introduction

Lowering low-density lipoprotein cholesterol (LDL-C) via lifestyle change or pharmacologic therapy can reduce the cardiovascular risk (CV) in patients with type 2 diabetes (T2D). However, the response to lipid-lowering interventions is not uniform and a significant proportion of T2D patients do not reach the recommended LDL-C target. Elucidating the factors associated with lipid goal attainment represents an unmet clinical need.

Material and method

This is a retrospective, cross-sectional study based on data from the Annals of the Diabetes Medical Association (AMD) database, which includes the electronic medical records of 1.186.247 patients treated in various Italian diabetes clinics between 2005 and 2019. In this study, we used Rulex®, a type of Logic Learning Machine (LLM) approach to extract and classify the most relevant variables that could predict the achievement of an LDL-C value below 2.60 mmol/l within two years (defined as T2Y) from the time of lipid therapy prescription (T0).

Results

Overall, 11.252 patients (45.46% female) with T2D and dyslipidemia were evaluated. Stratification according to CV risk showed that, at T0, 97.7% of patients were at very high risk and 2.3% at high risk. At T0, 95.79% of patients were prescribed statins, and only 9.16% ezetimibe. The treatment goal at T2Y was achieved in 61.4% of cases. The LLM model was endowed with a precision of 69% and an accuracy of 67% (AUC-ROC: 0.775, $P<0.001$) to predict the attainment of LDL-C target. LDL-C values at T0 and six months later (T6M) exhibited the highest significance in this predictive model. Other predictors identified by LLM were: uninterrupted treatment between T0 and T2Y, higher HDL-C levels, younger age, anti-hypertensive drug administration, lower glycosylated hemoglobin levels, a higher Q-score, a lower BMI, lower micro-albuminuria levels and male gender. For each of the initial LDL-C ranges analyzed, the LLM also indicated the minimum reduction that should be achieved by T6M to increase the probability of reaching the therapeutic goal within T2Y, thus offering a new helpful tool to guide the physician's therapeutic attitude.

Conclusion

This is the first study describing the application of a LLM approach on real-world data to identify variables involved in lipid goal attainment. Our results suggest that a follow-up visit should be recommended within six months after the start of lipid therapy in all T2D patients. The present study also underscores the importance of initiatives to establish a more aggressive lipid management strategy for specific patient subgroups.

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OC10.4

Establishing a regional registry for hyperosmolar hyperglycaemic state to share best practice: initial results and future implications

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Introduction

Hyperosmolar hyperglycaemic state (HHS) is an acute complication of diabetes which requires prompt recognition to prevent morbidity and death. Owing to its

low prevalence, clinicians report a lack of confidence in management, which may result in delayed diagnosis and worsened outcomes. The limited literature on HHS management means most guidelines are based solely on expert opinion, resulting in significant discrepancies between care in centres.
Aim
s: This study aimed to establish a registry of HHS cases in order to identify baseline HHS management, share best practices across hospitals and highlight areas for improvement.
Methods
The study retrospectively analysed patients with HHS from March 2021 to January 2023 across eight hospitals within the West Midlands. Cases were identified from patient notes using criteria from the Joint British Diabetes Societies (JBDS) HHS guidelines[1]: serum osmolality > 320 mOsmol/kg and glucose > 25 mmol/l. Osmolality was calculated using the formula [(2× sodium) + (2× potassium) + glucose + urea]. HHS resolution was documented as the earliest event of either serum osmolality falling below 300 mOsmol/kg, when fixed rate intravenous insulin infusion (FRIII) was stopped or when the team documented HHS resolution in the clinical notes. Patient demographics, precipitating cause of HHS and management regime were also collected. Data was analysed using SPSS and results presented as frequencies, median and interquartile range (IQR).
Results
68 cases of HHS were identified. 73.5% had the correct diagosis documented and just 42.6% had serum osmolality measured during stay. The most common causes of HHS were intercurrent illness (48.5%), sepsis (16.2%) and new diagnosis of diabetes (13.2%). Median serum osmolality at diagnosis was 352 mOsmol/kg (IQR: 334.63-375.07) and patients recieved a median of 6750 ml fluid (IQR: 4000-10500) until HHS resolution. 27.9% had FRIII commenced within the first hour of diagnosis and 51.8% were also given basal insulin. While the length of stay was similar for HHS across included hospitals, there was a significant difference in HHS duration between sites ($P < 0.001$).
Conclusion
These results suggest there is a need to improve awareness of HHS and the guidelines for its management amongst clinicians. By establishing a registry of HHS cases over several hospital trusts, best practices can be shared between healthcare professionals. Expanding the scope of this project to include other regions will allow uniform clinical care to be provided to HHS patients nationally.
Reference
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OC10.5

A study of 512 diabetes-related ketoacidosis episodes shows no added risk or impact on outcomes during Ramadan: Results from DEKODE study

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Background
With increasing ethnic diversity in the Western World, it is important to establish the safety of religious practices such as fasting during Ramadan. There is limited information about severity and outcome of diabetes-related ketoacidosis (DKA) during Ramadan outside Middle East.
Objective
We studied differences in severity, DKA-related complications and outcomes of DKA before (Shaban), during (Ramadan) and after Ramadan (Shawwal).
Methods
All DKA events in Shaban, Ramadan and Shawwal from 2014 to 2022 at various tertiary and regional hospitals in the United Kingdom participating in the DEKODE (Digital Evaluation of Ketosis and Other Diabetes-related Emergencies) were included in this study. The diagnosis of DKA was defined as per the national guidelines. DKA parameters at presentation and during management, were investigated according to timing of DKA episode, diabetes type, and ethnicity. Data were analysed using Stata/SE V.16.1 for Mac. Data was found to be non-normally distributed using Shapiro-Wilk tests. Skewed data were presented as median and IQR. Discrete data were summarised as number (%) and statistical comparisons were made using chi-squared tests. These parameters were further investigated in subgroup analyses according to timing of DKA episode (before, during, and after the month of Ramadan), diabetes classification (type 1 and type 2), and ethnicity (Black, White, Asian, Mixed, Other).
Results
512 DKA episodes were identified for this study. Excluding urea and serum osmolality, there were no differences at presentation of DKA during Ramadan compared to Shaban and Shawwal. There was no significant difference in the outcome of DKA as measured by DKA duration (Shaban vs Ramadan vs Shawwal: 14.3 (8.9-24.4) vs 15.1 (9.5-22.8) vs 15.3 (9.6-23.2) hours, $P = 0.800$) and length of stay (Shaban vs Ramadan vs Shawwal: 3.6 (1.9-8.8) vs 4.1 (2.1-8) vs 4.1 (2.1-9.7), $P = 0.670$). Also, there was no significant difference in the number of hypoglycaemias, hypokalemia and hyperkalemia associated with DKA management during Shaban, Ramadan and Shawwal. Overall, there were no year-based differences between the years of 2014 to 2022. People with T1DM had higher acidosis and more hyperglycaemic events during Shawwal compared to T2DM. Across ethnicity, South Asians had more severe DKA in Ramadan compared to Shaban and Shawwal.
Conclusion
In the largest of its kind study in the Western world, we demonstrate no difference in DKA frequency during Ramadan. The increased severity of DKA during Shawwal, particularly in people with T1DM, suggests future guidelines should focus on the period following Ramadan to mitigate risk.
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Oral Communications 11: Late Breaking

OC11.1

Copper-based therapeutics increase sodium/iodide symporter (NIS) transcription and enhance radioiodide uptake in thyroid cancer cells

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Introduction
New drug approaches are urgently required to improve radioiodide (RAI) uptake for efficient ablation of thyroid cancer cells in RAI-refractory disease. Employing high-throughput screening of FDA-approved compounds we recently identified drugs capable of robust induction of sodium iodide symporter (NIS) activity to promote RAI uptake[1]. In particular, a leading drug candidate – the well-established anti-alcoholism drug disulfiram (DSF) – had not been previously implicated in regulating NIS. A better understanding of how DSF can be used to modulate NIS function *in vivo* is now needed prior to clinical evaluation.
Materials and Methods
NIS function was monitored *in vitro* by RAI (^{125}I) uptake assays, and NIS expression via Western blotting and TaqMan-RTPCR. Technetium-99m pertechnetate (^{99m}Tc) uptake was used to evaluate NIS function in Balb/c mice following intravenous administration.
Results
We demonstrate that the ability of DSF to increase RAI-uptake in thyroid TPC-1 (3.1-fold; $P < 0.01$) and 8505C (4.9-fold; $P < 0.001$) cells can be significantly potentiated by combination with Cu^{2+} to 5.1-fold and 18.9-fold increases respectively. Despite promising data, DSF has poor bioavailability *in vivo* due to its rapid metabolism to diethyldithiocarbamate (DDC) within the stomach and circulation with subsequent methylation in the liver. Whilst methylated DDC did not have any effect on NIS function, DDC chelated to divalent copper ions [$Cu(DDC)_2$] was highly effective at increasing RAI uptake (up to 8-fold; $P < 0.001$) in multiple thyroid cell types and induced significant NIS protein expression (up to 36.2-fold; 250 nM; $P < 0.001$). Interestingly, a transcriptional effect of $Cu(DDC)_2$ was revealed via significant induction of NIS mRNA levels in TPC-1 (8.5-fold; $P < 0.001$) and 8505C (104.8-fold; $P < 0.001$) cells. In wild-type Balb/c mice the intraperitoneal administration of albumin nano-encapsulated

$Cu(DDC)_2$ significantly induced thyroidal uptake of technetium-99m (^{99m}Tc) after 30 min (~40% increase; $n=11$ per group; 3 mg/kg dose; $P<0.001$), as well as increasing thyroidal mRNA levels of NIS (1.9-fold; $P<0.01$), thyroid peroxidase (1.8-fold; $P<0.001$) and thyroglobulin (1.3-fold; $P<0.05$). Importantly, a significant positive correlation between thyroidal ^{99m}Tc uptake and higher NIS mRNA levels ($r_s=0.4477$, $P=0.0169$) was apparent in $Cu(DDC)_2$-treated mice. Additionally, thyroidal ^{99m}Tc-uptake ($P<0.05$) and NIS expression ($P<0.05$) were induced following intravenous administration of albumin nano-encapsulated $Cu(DDC)_2$ (~30%; $n=5$; 5 mg/kg dose).

Discussion

Our study demonstrates a promising drug strategy utilising a disulfiram metabolite to enhance NIS function *in vivo*, with clinical potential to improve treatment effectiveness in RAI-refractory thyroid cancer patients.

Reference

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OC11.2

Machine learning-based steroid metabolome analysis reveals three distinct subtypes of polycystic ovary syndrome and implicates 11-oxygenated androgens as major drivers of metabolic risk

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Introduction

Polycystic ovary syndrome affects 10% of women and comes with a 2-3fold increased risk of type 2 diabetes, hypertension, and fatty liver disease. Androgen excess, a cardinal feature of PCOS, has been implicated as a major contributor to metabolic risk. Adrenal-derived 11-oxygenated androgens represent an important component of PCOS-related androgen excess and are preferentially activated in adipose tissue. We aimed to identify PCOS sub-types with distinct androgen profiles and compare their cardiometabolic risk parameters.

Methods

We cross-sectionally studied 488 treatment-naïve women with PCOS diagnosed according to Rotterdam criteria [median age 28 (IQR 24-32) years; BMI 27.5 (22.4-34.6) kg/m^2] prospectively recruited at eight centres in the UK & Ireland ($n=208$), Austria ($n=242$) and Brazil ($n=38$). All participants underwent a standardised assessment including clinical history, anthropometric measurements, fasting bloods and a 2-hour oral glucose tolerance test. We quantified 11 androgenic serum steroids, including classic and 11-oxygenated androgens, using a validated multi-steroid profiling tandem mass spectrometry assay. We measured serum insulin to calculate HOMA-IR and the Matsuda insulin sensitivity index (ISI). Steroid data were analysed by unsupervised k-means clustering, followed by statistical analysis of differences in clinical phenotype and metabolic parameters.

Results

Machine learning analysis identified three stable subgroups of women with PCOS with minimal overlap and distinct steroid metabolomes: a cluster characterised by mainly gonadal-derived androgen excess (testosterone, dihydrotestosterone; GAE cluster; 21.5% of women), a cluster with predominantly adrenal-derived androgen excess (11-oxygenated androgens; AAE cluster; 21.7%), and a cluster with comparably mild androgen excess (MAE cluster; 56.8%). Age and BMI were similar between groups. As compared to GAE and MAE, the AAE cluster had the highest rates of hirsutism (76.4% vs 67.6% vs 59.9%) and female pattern hair loss (32.1% vs 14.3% vs 21.7%). The AAE cluster had significantly increased insulin resistance as indicated by higher values for fasting insulin,120 min insulin and HOMA-IR, and lower ISI than GAE and MAE clusters (all $P<0.01$). The AAE cluster also had a 2-3fold higher prevalence of impaired glucose tolerance and newly diagnosed type 2 diabetes.

Conclusion

Unsupervised cluster analysis revealed three PCOS subtypes with distinct androgen excess profiles. Women within the adrenal androgen excess cluster had a significantly higher prevalence of insulin resistance, impaired glucose tolerance and type 2 diabetes. These results implicate 11-oxygenated androgens as major drivers of metabolic risk in PCOS and provide proof-of-principle for an androgen-based stratification tool that could guide future preventative and therapeutic strategies in women with PCOS.

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OC11.3

Effects of semaglutide, PYY3-36, antagonists of the GLP-1/NPY-Y2 receptors, and empagliflozin on non-alcoholic fatty liver disease

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Background

Non-alcoholic fatty liver disease (NAFLD) is a common comorbidity in obese individuals. GLP-1 agonists, such as semaglutide, and SGLT-2 inhibitors, such as empagliflozin, are well known to be beneficial in NAFLD, while other incretins, like peptide tyrosine tyrosine 3-36 (PYY3-36), might be also useful for the treatment of NAFLD. We directly compared the effects of semaglutide alone and in combination with peptide tyrosine tyrosine 3-36 (PYY3-36), empagliflozin and semaglutide + empagliflozin as well as antagonists of GLP-1 and PYY on liver health.

Methods

High-fat diet (HFD)-induced obese male Wistar rats ($n=55$; mean weight 262 g) were randomized into the following treatment groups: semaglutide, semaglutide + PYY3-36, empagliflozin, semaglutide + empagliflozin, JNJ-31020028 (NPY-Y2 receptor antagonist), JNJ-31020028 + exendin 9-39 (GLP-1 antagonist), and saline. Animals had free access to high- and low-fat diet. Body weight and food preference were measured on a daily basis. After an observation period of 8 weeks, liver samples were histologically evaluated (modified Kleiner steatosis score for rodents, higher scores indicating higher grades of steatosis).

Results

Semaglutide and more pronounced semaglutide + PYY3-36 treatment led to weight loss, reduced overall food intake and (less pronounced) reduced high-fat preference compared to saline controls. Although less effective regarding food intake/body weight, semaglutide monotherapy revealed similar beneficial effects on the liver as semaglutide + PYY3-36, which had both antisteatotic effects (mean score 0.7 ± 1.2 for semaglutide alone and 0.2 ± 0.5 for the combination). Empaglifolzin had no effects on body weight and food preference, but was effective in reducing steatosis alone (mean score 0.8 ± 0.8) and more pronounced in combination with semaglutide (mean score 0.0 ± 0.0). JNJ-31020028, an antagonist of the NPY-Y2 receptor, and the combination of JNJ-31020028 and exendin 9-39 led to an increased high-fat diet preference and to the worsening of steatosis compared to saline treatment (mean score 2.3 ± 0.6 in both groups).

Conclusions
Semaglutide, semaglutide + PYY3-36 combination therapy, empagliflozin, and semaglutide + empagliflozin are highly effective in improving liver health. Interestingly, treatment with GLP-1 and PYY (NPY-Y2-R) antagonists led to the aggravation of hepatic steatosis. This underlines the potential of GLP-1 and PYY-36 agonists in the treatment of obesity and related NAFLD. The positive effects of empagliflozin on liver health, however, seem to be independent of body weight and food preference. Further approaches will go for underlying mechanistical aspects.

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OC11.4

Persistence of mild hypercortisolism in patients with Cushing's disease treated with cortisol-lowering drugs : the Haircush study

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Background
Medical treatment with cortisol-lowering drugs is commonly used following pituitary surgical failure or recurrence of hypercortisolism in patients with Cushing's disease (CD). Studies using late-night salivary cortisol (LNSF) measurement have shown persistent disruption of the circadian secretion of cortisol despite normalization of UFC in a subset of medically treated CD patients.Study aim Our objective was to assess the long-term cortisol exposure in CD patients medically treated using hair-cortisol (HF) and hair-cortisone (HE) measurement.
Study design
The Haircush multicenter prospective study included three groups (G) of females with a history of CD: G1 = 16 patients with normal UFCs following medical treatment with a stable drug dosage of osilodrostat, metyrapone, ketoconazole, pasireotide or cabergoline; G2 = 13 control patients in remission following pituitary surgery and with a normal pituitary-adrenal function; G3 = 15 control patients receiving stable recommended doses of hydrocortisone (15-25 mg/d) following bilateral adrenalectomy (BLA). Patients were evaluated during 3 months with their usual treatments. Two late-night saliva and 24 h urine samples were collected in G1 patients every month and only at the end of the study end in G2 and G3 patients. A clinical examination and 3-cm hair sample was collected at the end of the study in all patients. The outcome measures were a clinical Cushing's score and centralized measurements of HE, HF, LNSF and late-night salivary cortisone (LNSE), and UFC using LC – MS/MS.
Results
Despite having almost all UFCs within the normal range, G1 patients had increased HE concentrations as compared to G2 controls ($P = 0.003$). G1 patients also had increased clinical score ($P = 0.001$), UFC ($P = 0.03$), LNSF and LNSE ($P = 0.0001$) and increased variability in the latter parameters ($P = 0.004$). G3 patients with BLA had increased HF ($P = 0.002$) and HE (p = 0.003) compared to G2 controls contrasting with similar LNSE. Six of the 15 G1 patients exhibited increased HE concentrations above the range of G2 controls and had increased requirement of antihypertensive drugs compared to G1 patients with normal HE ($P = 0.05$).
Conclusion
A single HE measurement identifies chronic mild persistent hypercortisolism in a subset of medically-treated CD patients despite normalized UFCs. Persistent hypercortisolism was at least partly due to an altered circadian rhythm of free serum cortisol. HE could replace multiple saliva and urine analysis to assess the control of hypercortisolism in medically treated CD patients once UFC is normalized. Our results also suggest that patients treated with BLA should receive lower hydrocortisone dosage than that usually prescribed.

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OC11.5

Calcium and vitamin D supplementation in rats with sulpiride-induced hyperprolactinemia

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Background
Hyperprolactinemia, caused by chronic use of antipsychotics, is associated with impaired bone density and increased risk of fractures. We examined if calcium and vitamin D supplementation have influence on Prlr gene expression in the duodenum, vertebrae and kidneys in female rats with sulpiride-induced hyperprolactinemia.
Methods
Wistar female rats 21 weeks old were divided into: Group S: 10 rats that were intramuscular administrated Sulpiride (10 mg/kg) twice daily for 6 weeks; Group D: 10 rats that were administrated Sulpiride (10 mg/kg) twice daily for 6 weeks, calcium 50 mg daily and vitamin D 500 IU per day for last 3 weeks; and age matched nulliparous rats as a control group: 7 rats, 21 weeks old (C). Laboratory analysis included measurements of serum ionized calcium, phosphorus, urinary calcium and phosphorous excretion, osteocalcin (OC), vitamin D, and prolactin. Relative quantification of prolactin receptor (*Prlr*) gene expression in duodenum, vertebrae and kidneys was determined using real-time PCR.
Results
PRL concentrations were significantly higher in group S and D, compared to C ($P < 0.001$). Ionized calcium was significantly increased in the group S compared to C ($P < 0.001$) and without significance between group D and C. Serum phosphorus was not significantly changed in S and D compared to C. Urinary calcium was decreased in group S compared to C but without significance and significantly increased in D compared to C ($P < 0.001$); urinary phosphorous was not significantly changed neither in S nor in D. OC was significantly decreased in group D compared to C ($P < 0.001$) and without significance between groups S and C. Expression of the Prlr gene was significantly lower in the duodenum ($P < 0.01$) and higher in vertebrae and kidneys in the sulpiride-induced hyperprolactinemia (S) than in the control group. Significantly higher Prlr expression in the duodenum was verified ($P < 0.01$), along with increased Prlr gene expression in vertebrae and kidneys, in rats with sulpiride-induced hyperprolactinemia and calcium and vitamin D supplementation, than in the C group.
Conclusions
In sulpiride-induced hyperprolactinemia, down-regulation of Prlr gene expression in duodenum could be underlying reason for diminished intestinal calcium absorption. In order to maintain calcium homeostasis, since intestinal absorption is compromised, prolactin will rapidly take calcium from skeletal system, thanks to increased Prlr gene expression in the vertebra. Calcium and vitamin D supplementation in the sulpiride-induced hyperprolactinemia significantly increased Prlr gene expression in duodenum which could improve intestinal calcium absorption and reduce the harmful effect on the bone system.

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OC11.6

Assessment of clinical and histopathological predictors for remission after transsphenoidal surgery for acromegaly

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Background
Transsphenoidal surgery (TSS) is the primary treatment of choice in acromegaly. Previous research succeeded to some extent in predicting remission after TSS. However, it was based mainly on clinical and radiological data, lacking histopathological evaluation.
Objective
To produce a clinicopathological prediction model for remission after TSS for acromegaly, enabling clinicians to better inform patients on expected treatment outcome.
Design
Single-center study with retrospective data collection on patients with acromegaly in a large tertiary referral center in The Netherlands. Overall, 100 patients with acromegaly in whom TSS was performed as primary therapy between January 2000 and July 2019 were included.
Methods
Data were collected on sex, age, biochemistry (IGF1, GH nadir during OGTT, random GH) at diagnosis, 3 months to 1 year postoperatively and at last visit, use of preoperative medication, applied postoperative treatment (repeated surgery, radiotherapy and medical therapy), tumour subtype according to the WHO 2017 classification and proliferation markers (Ki-67, p53 and mitotic index). All available diagnostic and first postoperative MRI's were reassessed by an

experienced neuroradiologist and classified according to the Knosp classification. In addition, tumour volume (cm3), maximum tumour diameter (mm) and T2-weighted MRI signal were determined. Uni- and multivariate regression models were used to identify predictors of early biochemical remission (12 weeks to 1 year postoperatively) according to the consensus criteria and long-term remission (age- and sex-normalized IGF1, absence of postoperative treatment until last follow-up and absence of a tumour remnant on postoperative MRI).
Results
Median duration of follow-up was 11.8 years from diagnosis and 11.1 years from surgery. Forty-six (46.5%) patients were found to be in early biochemical remission, forty-one (42.7%) were in long-term remission. In univariate logistic regression larger tumour volume (odds ratio [OR] 0.86, $P=0.023$), larger maximum tumour diameter (OR 0.85, $P<0.001$), higher modified Knosp classification grade (OR 0.44, $P<0.001$), presence of cavernous sinus invasion (OR 0.054, $P=0.006$) and higher random GH at diagnosis (OR 0.98, $P=0.008$) were significantly associated with lower remission rates. In multivariate logistic regression, a simple model with only maximum tumour diameter as independent variable predicted best for both early biochemical remission (OR 0.85, 95% CI 0.78-0.93, $P<0.001$, sensitivity 78.9%, specificity 71.8%) and long-term remission (OR 0.75, 95% CI 0.66-0.86, $P<0.001$, sensitivity 79.4%, specificity 78.0%).
Conclusion
maximum tumour diameter is the best predictor for remission after TSS for acromegaly in this single center cohort.

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Oral Communications 12: Environmental Endocrinology

OC12.1

Androgen Receptor Binding by DDE at the BF3 Site Favors Release of Bound Dihydrotestosterone

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The androgen receptor (AR) function is inhibited by endocrine disrupting chemicals (EDCs) such as DDT and DDE leading to problems in embryonic development and negative health outcomes for adults. EDCs may bind in the steroid binding pocket and disrupt AR function by leading to altered receptor conformations. However, this may not be the only way EDCs interfere with the receptor. Estébanez-Perpiñá et al identified binding function 3 (BF3) as a surface binding site for small hydrophobic compounds that disrupted AR activity. We found that DDT, DDE, and related compounds induced the release of bound dihydrotestosterone (DHT) from the AR ligand binding domain with IC50 values ranging from 54 to 82 μM. In addition, mutant AR genes with single amino acid changes in the BF3 site showed a reduced sensitivity for the ability of DDE to disrupt AR activity *in vivo* using a reporter assay. These results suggested that DDE interacts with the BF3 site and allosterically regulates AR activity. We used molecular dynamics (MD) simulations methods to test whether DDE bound to BF3 induces allosteric changes in the AR structure, altering the dynamic behavior of AR with bound steroid. Accelerated MD simulations identified possible exit pathways for DHT and steered MD simulations showed that the free energy of steroid unbinding was decreased for the exit pathways studied when DDE was bound in the BF3 site. These results suggested that AR dynamics are impacted by DDE interacting with the BF3 site, destabilizing the steroid in its binding pocket and reducing the energy required for steroid release, thus disrupting AR function.

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OC12.2

Effect of circadian disruption on the hypothalamic control of reproduction in female mice

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In female mammals, the timing of the preovulatory LH surge depends on the combination of the positive estrogen feedback and a circadian signal which synchronizes the LH surge with the transition between the resting and active period at the end of the follicular phase, when arousal is maximal. Previous results have demonstrated that a functional biological clock, located in the suprachiasmatic nucleus (SCN), is required for optimal female fertility. In this context, we have investigated the consequences a chronodisruptive environment could have on the female mammals' gonadotropic axis using a female mouse model of shiftwork. This is a relevant issue since an increasing number of women are working in non-standard work schedules in our modern 24 h/7 d society, and shift work is associated with reproductive deficits. Adult female mice were either kept in regular light/dark schedules or exposed to a model of shift work conditions (3 weeks rotation a 10-hour phase advance for three days and a 10-hour phase delay for four days). Daily rhythms in SCN vasopressin-containing neurons, kisspeptin neurons, LH secretion on the day of proestrus, as well as fertility parameters, were compared between both groups of mice. The chronodisruptive protocol reduces the number of the vasopressin neurons known to transmit the daily information to the kisspeptin neurons, abolished activation of kisspeptin neurons typically observed at the light/dark transition, and reduced the amplitude and altered the timing of the preovulatory LH surge. Furthermore, when female mice exposed to chronic shift are mated with a male, the number of gestation is reduced as compared to those observed in control female mice. Our results indicate that chronic shift desynchronizes the hypothalamic-pituitary-ovarian axis. Notably, chronic exposure to disrupted light/dark cycles impairs the vasopressin-induced daily activation of kisspeptin neurons which can explain the altered LH secretion and the reduced fertility in female mice. In future experiments, we will investigate whether peripheral clocks within the gonadotropic axis are also altered by chronic shift. Altogether, these experiments will provide a better understanding of circadian disruption's potential on the daily reproductive rhythms of female mammals.

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OC12.3

Effects of perinatal tributyltin exposure in Wistar rats on body parameters, insulin, leptin, milk composition and ultrastructure of the pancreatic islets in dams and offspring

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Tributyltin (TBT) is a biocide organotin compound widely used as an antifouling in boat paints. This substance is a factor of contamination to water and food, especially marine fish. As an endocrine disruptor, TBT can interact with hormonal pathways and can induce gonadal dysfunction and glycemic dyshomeostasis; however, the effects caused by maternal exposure to TBT are scarce. Here, we investigate maternal exposure to low dose of TBT, considered safe, during pregnancy and lactation on the metabolism of dams as well as male and female offspring. For this, pregnant Wistar rats were exposed on the 7th day of gestation until weaning (21st day of lactation) by gavage to vehicle (0.1% ethanol, Control group) or TBT (100 ng/kg of body weight, bw, TBT group). Morphometric parameters, milk composition and plasma hormone profile from dams and offspring at birth and weaning were evaluated. Analyses of the fragments of pancreas were performed by Transmission Electron Microscopy (TEM) at weaning. Ethical protocol: CEUA/010/2019. Student t test was used to statistical analyses ($n=8$/group). In dams, TBT exposure increased the body fat at the end of pregnancy ($+38\%$, $P=0.007$). In the milk, total protein and cholesterol contents were increased ($+18\%$, $P=0.03$ and $+73\%$, $P=0.01$, respectively), lactose was reduced (-30%, $P=0.03$), but insulin and leptin was unaltered at weaning. Regarding the offspring, females had reduced bw and nasoanal length at birth (-8%; $P=0.003$; -10%; $P<0.0001$, respectively), while the males did not show changes of these parameters. Offspring from both sexes have delayed eye opening during development. Only female offspring showed decreased plasma insulin and leptin levels at weaning (-43%; $P=0.03$; -45%; $P=0.04$, respectively). The pancreatic islets of dams and offspring from both sexes showed few preserved mitochondria, many granules with crystallized insulin scattered throughout the cytoplasm and endoplasmic reticulum with dilated cistern regions, indicating a reticulum stress process. The amount of our data evidence that tributyltin exposure during gestation and lactation alters insulin and leptin levels of female offspring and causes pancreas impairment in dams and offspring from both sexes at weaning. Thus maternal TBT exposure at a low dose affects mothers and offspring suggesting the development of future chronic diseases, as diabetes mellitus.

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OC12.4

Micronutrient deficiency screening in obese patients

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Background and Aim
A direct link between obesity and micronutrient deficiencies has been established. These nutritional dificencies are mainly caused by poor-quality diets but also due to increased demands and have been associated with a wide range of physiological and functional impairments. The aim of this study was to assess the nutritional status of obese patients and to investigate the possible association between funnctional disorders and micronutrient intake.
Methods
This is a cross-sectional descriptive study including 50 obese patients.Dietary intake was assessed by trained nutritionists using a 24-hour recall method. Functional disorders were detected by the Screening of Micronutrient Deficiency (DDM) questionnaire validated by the European Institute of Dietetics and Micronutrition (IEDM) that evaluates mood, gastro-intestinal, osteoarticular, infectious, skin and circulatory disorders. Statistical associations between the questionnaire's results and dietary intake were assessed using the SPSS 25.0 version.
Results
Mean age was 41, 54 ± 12, 48 years with female predominance (88%). Mean BMI was 40.33 ± 6.39 kg/m^2. Vitamin A, D, C, and B6 deficiency was noted in 74%, 100%, 96% and 68% of cases, respectively. Magnesium, iron, zinc, copper, and selenium deficiency was noted in 82%, 6%, 24%, 22% and 8% of cases, respectively. There were a significant and negative association between fatigue, mood disorders and vitamin B6 and magnesium intake ($r = -0.485$; $P < 0.01$ and $r = -0.292$; $P = 0.039$, respectively), osteoarticular and degenerative disorders and vitamin A intake ($r = -0.297$; $P = 0.036$), infectious disorders and vitamin C, selenium and iron intake ($r = -0.368$; $P = 0.09$, $r = -0.336$; $P = 0.017$ and $r = -0.292$; $P = 0.04$, respectively), skin diseases and beta-carotene intake ($r = -0.344$; $P = 0.014$) and circulatory system diseases and vitamin B9 intake ($r = -0.394$; $P = 0.005$). Gastrointestinal disorders were not significantly associated with dietary intake.
Conclusion
Evaluating micronutriment deficiencies is an important step in identifying the underlying cause of many chronic symptoms and conditions in obese patients in order to improve their treatment and quality of life.

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OC12.5

Pregnant women in the Faroe Islands are iodine depleted

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Introduction
Iodine deficiency is a significant global health issue of various severity depending on the age of the deficiency. The foetal period is the most critical stage in life, negatively impacting the brain and neurodevelopment. Hence, the developing foetus is a crucial issue, and the present study focussed on iodine nutrition among pregnant women from the Faroe Islands. The need for iodine increases in pregnancy, and the recommended target for median urinary iodine concentration is 150-250 µg/l.Method: We recruited 630 participants in a nationwide, cross-sectional study of pregnant women. They were primarily Caucasian women referred to routine obstetric ultrasound from 2020 through 2022 in gestational week 18. Participants donated a spot urine sample and completed an iodine-specific questionnaire. Iodine was determined using the Sandell-Kolthoff reaction modified according to Wilson and van Zyl.
Results
The participation rate was 70%. The overall median urinary concentration was 110 µg/l for the two years of collecting data. Interestingly, the median UIC decreased from 121 µg/l during the first year of inclusion to 96 µg/l during the second year ($P < 0.01$). Conversely, the number of samples in the excessive range decreased from 9.1% to 3.6% ($P < 0.001$). Dietary data are underway.
Conclusion
The marked change over time raises concerns about the validity of cross-sectional studies of iodine nutrition with short-term data collection. The time trend may have several explanations, including a change in the intake of local foods rich in iodine, which needs follow-up. Finally, according to the WHO recommendations, our nationwide study demonstrated that Faroese pregnant women were iodine depleted.

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OC12.6

Effects of perinatal exposure to endocrine-disrupting chemical Tetrabromobisphenol A on neurodevelopment in mice

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Tetrabromobisphenol A (TBBPA) is a brominated flame retardant and is widely used in electronic goods, plastics and furniture. TBBPA is frequently detected in water, soil, organisms and even in human breast milk. It is accessible to both the developing fetus and the nursing pups following maternal exposure. Though some regulatory agencies have asserted that consumer exposures to TBBPA are unlikely to have adverse implications for human health, the safety of TBBPA has been questioned. Reported evidence of endocrine-disruption of TBBPA in brain has raised concerns regarding its effects on neurodevelopment and behavioral functions. The present study examined the effects of exposure to TBBPA on neurodevelopment. The Developmental Neurotoxicity Test(DNT) was performed to determine whether TBBPA is a developmental neurotoxicant. Additionally, maternal mice were administered 0, 0.24 and 2.4 mg/kg TBBPA. Mice offspring underwent behavior tests for assessment of locomotor, depressive, compulsive, cognitive, and social behaviors. Gene expression pattern change at transcriptional level in the brain was investigated with real-time PCR. As a result, we classified TBBPA as a developmental neurotoxicant from the DNT. In addition, the TBBPA-treated mice offspring showed abnormalities in motor activity, compulsive-like behavior, social interaction patterns and spatial learning. Aberrant gene expression, such as acetylcholinesterase (AChE) and tyrosine hydroxylase (TH), were found in the perinatal TBBPA-treated mice offspring brain. To summarize, these findings suggest that perinatal exposure to TBBPA interferes with brain development and behavioral functions in mice. Therefore, it is necessary to pay more attention to the potential effects of TBBPA in the early development of brain.

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OC12.7

Polychlorinated biphenyls (PCBs) modulate AHR pathways leading to the altered expression of genes involved in extra-cellular matrix (ECM) remodeling and epigenetic regulation in thyrocytes

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Background
PCBs are chemical pollutants able to promote inflammation and carcinogenesis. They can accumulate in human tissues through the food chain causing a variety of adverse health effects. The NF-E2 p45-related factor 2 (NRF2) and the aryl hydrocarbon receptor (AHR) are ligand activated transcription factors controlling pathways modulating xenobiotic metabolism. Increasing evidence indicate the involvement of AhR in regulating extracellular matrix (ECM) homeostasis. ECM is a complex network of multidomain macromolecules. Endothelial cell-specific molecule 1 (ESM-1), a soluble dermatan sulfate proteoglycan, also known as endocan, is up-regulated in different pathological conditions, including cancer, driving tumor progression, tumor vascularization and metastasis. In the landscape of non-coding RNAs, the long-non coding RNAs (>200 nucleotides) are a new class of epigenetic regulators that play a key role in homeostatic and pathological mechanisms, especially in cancer.Purpose. The present study was aimed at investigating the effects of dioxin-like pentachlorobiphenyls (PCBs) on aryl hydrocarbon receptor (AHR)/nuclear factor erythroid 2 – related factor 2 (NRF-2) pathway and related long noncoding RNAs (lncRNAs) and endothelial cell-specific molecule 1 (ESM-1) in thyrocytes.

Methods
Primary human thyrocytes were exposed to increasing doses (5 and 10 μM) of 2,3′,4,4′,5-pentachlorobiphenyl (PCB-118) and 3,3′,4′,4′,5 pentachlorobiphenyl (PCB-126) for 24 h. Cell culture and medium were collected to assess: mRNA levels of AHR, NRF-2, CYP1A1, lncRNAs (HOTAIR, MALAT-1, MEG-3), ESM-1, metalloproteinases (MMP) -3, MMP-9 and IL-1β by qPCR; protein levels of AHR and ESM-1 by western blot and ELISA, and ROS production by a commercial kit.
Results
Treatment with PCB-126 and PCB-118 at both doses after 24 h significantly increased mRNA levels of AHR, NRF-2, CYP1A1, MMP-3, MMP-9, IL-1β and intracellular ROS accumulation. Furthermore, PCBs, especially PCB-118, enhanced ESM-1, HOTAIR and MALAT-1 expression and reduced MEG-3 mRNA levels. Furthermore, AHR and ESM-1 protein levels increased after PCB-126 and PCB-118 exposure at both concentrations in a dose dependent manner.
Discussion
Our data demonstrated that PCB-118 and PCB-126 may induce AHR/NRF-2 pathway activation with a consequent ROS production and inflammatory responses in thyrocytes. This condition led to an increase in ESM-1, a circulating proteoglycan involved in angiogenesis and overexpressed in several tumors, and MMP-3 and MMP-9 that cause ECM remodeling. Furthermore, PCBs can induce epigenetic modifications by increasing lncRNAs MALAT-1 and HOTAIR expression and reduce anti-oncogenic lncRNA MEG3.
Conclusion
These results suggest new mechanisms underlying toxic effects of PCBs exposure on thyrocytes, indicating ESM-1 and lncRNAs as putative key factors of thyroid tumorigenesis.

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OC12.8

Bisphenols in adrenocortical cell culture: Further evidence for the relevance of endocrine disruptive chemicals for adrenal gland functionality

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Background
Bisphenol A (BPA) is known to act as an endocrine disruptor in different organs. However, its impact on adrenal gland functionality is largely unknown. This also applies to its substitute substances bisphenol F (BPF) and S (BPS). Therefore, experiments addressing this subject are urgently needed.
Methods
The human adrenocortical cell lines NCI-H295R and MUC-1 were treated with increasing concentrations (1 nM – 1 mM) of bisphenol A, F, and S. Concentrations of fifteen adrenal steroids in cell supernatants were measured via liquid-chromatography-tandem-mass spectrometry (LC-MS/MS) after different periods of exposure (24 h, 72 h). Cell viability was monitored to assess cytotoxicity.
Results
All tested bisphenols inhibit steroid production significantly compared to untreated cells in a dose- and time-dependent manner in both cell lines: in the NCI-H295R hormone levels of 11-deoxycortisol, testosterone, androstenedione, dihydrotestosterone and cortison were significantly decreased after 72 hours of exposure (at $>$ 100 μM BPA and BPF respectively, $P<0.05$). For instance, 100 μM BPA treatment resulted in a 0.29-fold decrease of testosterone, and a 0.43-fold decrease of cortison. Interestingly, BPA and BPF showed ambiguous effects on some parameters, e.g. a 0.39-fold decrease of progesterone was detected in 100 μM BPA, while BPF led to a 26-fold increase. Furthermore, we found an increased level of estradiol, 21-deoxycortisol and 17-hydroxyprogesterone in BPF-treated cells ($P<0.05$). The same experiments are currently performed for BPS. At large, reported effects were confirmed in MUC-1 cells, which seem to be more resilient against tested bisphenols. In this sense, calculated median lethal doses (LD50) were: BPA 110.1 μM, BPS 229.4 μM, BPF 344.5 μM for NCI-H295R and BPA 279.4 μM BPF 356.8 μM and BPS 1.31 mM for MUC-1.
Conclusions
Our results provide further evidence that bisphenol A, F, and S act as disruptors of steroidogenesis and steroid secretion. Underlying mechanisms and pathways are still widely unknown. This reinforces the need for further research efforts focusing on EDCs' effects on the adrenal gland.

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Rapid Communications

Rapid Communications 1: Diabetes, Obesity, Metabolism and Nutrition 1

RC1.1

Increased risk of erythrocytosis in men with type 2 diabetes treated with combined sodium-glucose cotransporter-2 inhibitor and testosterone replacement therapy

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Purpose of Study
Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) and testosterone replacement therapy (TRT) can increase red blood cell production through different mechanisms. Little is known if combination therapy poses risk of erythrocytosis (ERY) in real world clinical practice.
Methods
This was a retrospective nationwide cohort study of US Veterans with type 2 diabetes (T2D) without prior history of ERY who were prescribed SGLT-2i and/or TRT between 3/2013 – 10/2022, had no missing medical records data, and had adequate adherence based on the proportion of days covered >80%. Patients were divided into 3 groups: SGLT-2i only, TRT only, or combination. Odds Ratio (OR) of new ERY defined as hematocrit (Hct) level>54% within 365 days of therapy initiation was calculated by logistic regression model adjusted for case-mix. This study was approved by the IRB of Stratton VAMC, Albany, NY.
Results
Baseline clinical and biochemical characteristics were well balanced among the groups except higher rate of uncontrolled T2D in the SGLT-2i group and lower obstructive sleep apnea (OSA) prevalence in the TRT group (Table). Of the entire cohort, total of 732 (1.4%) patients developed ERY. In models adjusted for baseline Hct, age, BMI, OSA, diuretic use, and smoking status, patients on combination therapy had significantly higher odds of ERY compared to those on SGLT-2i (OR 3.86, 95% CI (2.35 – 6.12)) or TRT alone (OR 2.05, 95% CI (1.29 – 3.09)). The unadjusted ORs were comparable as well. The odds of developing ERY in each group were independent of baseline Hct.
Conclusions
For the first time, we demonstrated that in large cohort of patients combined therapy with SGLT-2i and TRT is associated with increased ERY risk compared with either treatment alone. Given rising prevalence of SGLT-2i use, providers should consider periodic Hct assessment in persons receiving both SGLT-2i and TRT.

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RC1.2

Utility of urinary metabolomic signatures to differentiate biopsy confirmed diabetic and non-diabetic kidney disease

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Background
Renal involvement in T2DM can be due to diabetes per se (Diabetic Kidney Disease) or causes other than diabetes (non-diabetic kidney disease). Currently available clinical, biochemical, and radiological markers fail to differentiate DKD from NDKD. Renal biopsy remains gold standard for diagnosis. Urinary signatures may provide a non-invasive alternative to that end. In cell culture and in animal models with diabetes and kidney disease, dysregulation of several metabolites has been reported. This has not been explored in humans with biopsy-proven kidney disease DKD and NDKD subjects.
Aims
To identify the expression of urinary metabolic signatures as putative marker for differentiation of biopsy-confirmed DKD and NDKD subjects.
Methods
Consecutive patient with renal involvement (eGFR >30 ml/min/m^2 to <60 ml/min/m^2 and/or ACR>300 mg/ mg) were subjected to biopsy and classified as per ISN/RPS Classification. We also recruited subjects with T2DM without nephropathy (eGFR >60 ml/min/m^2 and ACR<30 mg/ mg) for comparison. Morning urine sample were collected for analysis by Gas Chromatography and mass spectrometry. Features were extracted and analysed using appropriate statistical method.
Results
We recruited first 110 subjects who agreed to undergo renal biopsy. Among those 110 subjects, 73 (66.4%) had DKD; 20 (18.2 %) had NDKD; and 17 (15.4 %) had mixed kidney disease. We included only those with pure DKD or NDKD and T2DM subjects without nephropathy for analysis of urinary metabolomics. Urinary metabolites (M1, M2, M3, M4) were found to be depleted in patients with kidney disease (both in DKD and NDKD as compared to T2DM ($P<0.004$, $P<0.006$, and $P<0.01$, <0.03 respectively). M5 was exclusively depleted in NDKD. Level of M6($P<0.01$), M7($P<0.03$) was increased and M8($P<0.05$), M9($P<0.03$), M10($P<0.02$) was decreased in DKD subjects. Analysis of fragmentation pattern indicated that theSemetabolites putatively belong to central carbon metabolism, fatty acid metabolism, purine metabolism in addition to metabolites exclusively of non-endogenous (microbial) origin.
Conclusion
Urinary metabolomics analysis may help to distinguish DKD and NDKD subjects. Our results warrant validation in another cohort.

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RC1.3

Sex specific associations of serum selenium and selenoprotein P with type 2 diabetes mellitus and hypertension in the Berlin Aging Study II

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Objective
The aim of this study was to investigate sex-specific associations of two established serum selenium biomarkers, i.e. total selenium and selenoprotein P with type 2 diabetes mellitus (T2D) and hypertension in a large cohort of older people.
Methods
1500 participants with available selenium measurements from the Berlin Aging Study II (BASE-II) were included in this study. In the serum samples, spectroscopy was used to quantify total selenium, and ELISA was used to measure selenoprotein P. T2D was diagnosed based on antidiabetic medication, self-reported T2D, or laboratory parameters. Hypertension was diagnosed based on self-report, blood pressure measurements, or anti-hypertensive medication. Dose-dependent associations were quantified applying multiple adjusted regression models.
Results
The median (interquartile range) age of the cohort was 68 (65,71) years, and 767 (51%) of the participants were women. 191 (13%) participants were diagnosed

Table.

Variable	All Patients(n=53075)	SGLT2i Only (n=11712)	TRT Only (n=40769)	Both (n=594)	Effect Size
Age, yrs (Mean±SD)	62.54 (9.26)	65.51 (8.67)	61.69 (9.25)	61.77 (8.80)	0.01
BMI, kg/m^2 (Mean±SD)	34.15 (6.59)	34.03 (6.19)	34.16 (6.70)	35.86 (6.16)	0.00
White Race,% (n)	74.2 (39379)	78.5 (9195)	72.9 (29728)	76.8 (456)	0.05
Black Race,% (n)	15.2 (8068)	12.1 (1413)	16.1 (6569)	14.5 (88)	0.05
Hematocrit,% (Mean±SD)	41.37 (4.02)	41.81 (3.78)	41.22 (4.08)	42.64 (3.61)	0.08
Hemoglobin A1c,% (Mean±SD)	7.49 (1.51)	8.54 (1.22)	7.18 (1.45)	8.31 (1.20)	0.04
OSA,% (n)	25.6 (13564)	37.3 (4371)	21.8 (8869)	54.5 (324)	0.16
Diuretic use,% (n)	39.5 (20945)	38.1 (4468)	39.8 (16243)	39.8 (234)	0.01

with T2D and 1126 (75%) were diagnosed with high blood pressure. Total selenium and selenoprotein P displayed a statistically significant, positive correlation (r= 0.59, $P< 0.001$), and both selenium and selenoprotein P were elevated in those with self-reported Se supplementation. In the whole cohort, selenium and selenoprotein P were not associated with T2D. In men, selenoprotein P displayed a positive association with T2D, and the odds ratio (OR) (95% confidence interval (CI)) for one unit (mg/dl) increase in selenoprotein P was 1.22 (1.00, 1.48). In the whole cohort, selenium was non-linearly associated with hypertension, and comparing to the lowest quartile (Q1), participants with higher selenium levels (Q3) had a lower OR (95% CI) of 0.66 (0.45, 0.96). In sex-specific analyses, this finding proved to be specific for men. Selenoprotein P was positively associated with hypertension, OR (95% CI) per one unit increase (mg/dl) was 1.15(1.01,1.32).

Conclusions

The noted independent and dose-dependent associations suggest a potential role of Se status in the risk of T2D and hypertension in older subjects, with differences in associations based on sex and the selenium biomarker assessed.

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RC1.4

Angiotensin-converting enzyme in type II diabetes: effects of combined training on cardiovascular components and blood components

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Objectives

The angiotensin-converting enzyme (*ACE1*) gene is one of the most studied genes in the pathogenesis of type II diabetes (T2DM) and cardiovascular disease. However, in the context of exerciSemodels in T2DM, they are not yet fully understood. We intended to characterize the genetic profile of individuals with T2DM from an inter-individual point of view using prognostic markers and cardiovascular risk. On the other hand, relate it with the profile obtained with the type of training: high-intensity intervals (HIIT) with resistance (RT); and moderate continuous (MCT) with RT.

Methods

Subjects with T2DM ($n=80$, 59 years old) underwent a 1-year randomized clinical trial (clinicaltrials.gov ID:NCT03144505) and were randomized into three groups (control, $n=27$; HIIT with RT, $n=25$; MCT with RT, $n=29$). Biochemical parameters were determined by ELISA or standard methods at baseline and after 1 year of follow-up. *ACE1* I/D genetic polymorphism was determined by PCR-RFLP.

Results

After 1 year, training had implications for c-peptide, insulin levels and basophil percentage in T2DM. Interestingly, although no differences were observed in the distribution of *ACE1* genotypes, we observed that *ACE1* DD (versus ID+II) individuals showed changes in VO2 max percentages, both in the initial phase of the study and after 12 months of training and follow-up. This finding may be related to a state of pseudo-hypoxia, due to aldosterone dysregulation and concomitant increase in sodium reabsorption in T2DM. When we used the Mendelian randomization model, that is, selecting the DD genotype of *ACE1*, we verified that individuals submitted to HIIT (versus control) presented alterations both in the percentage of monocytes, as in the mean of mean globular hemoglobin and mean corpuscular volume ($P<0.05$). On the other hand, in the same model, but for the MCT, we only verified that the DD individuals from *ACE1* presented alterations in the number of platelets at the end of the training period.

Conclusions

Some blood count components have been associated with cardiovascular risk in patients with T2DM. With this study, we observed a differential profile between patients with *DMII* in the cardiovascular component possible related with *ACE1* polymorphism.

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RC1.5

Continuous subcutaneous insulin infusion (CSII) and growth in children with type 1 diabetes

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Introduction

Type 1 diabetes (T1D) is the most frequent children's endocrinopathy in Portugal. The duration of the disease and metabolic control may affect the final height of pediatric patients. Despite the metabolic advantages of technological advances, such as continuous subcutaneous insulin perfusion (CSII), the effect on growth is unclear.

Aim

To assess the impact of T1D treatment, with multiple daily injections (MDI) or CSII, on growth.

Materials and methods

Retrospective study with T1D patients born between 1996 and 2004. Considering 2 therapeutic groups (MDI vs CSII), patients were evaluated regarding age and pubertal Tanner stage at diagnosis, duration of T1D, metabolic control, presence of other autoimmune diseases, height and standard deviation (SD) at diagnosis and at age 18 and Mid Parental Target Height (MPTH). To compare growth between groups, the difference between the height SD at 18 years and MPTH SD was used (DifSD).

Results

From 131 patients, 52.7% were males ($n=69$). The mean age at T1D diagnosis was 9.4 ± 4.3 years, mean disease duration was 8.6 ± 4.3 years and total HbA1c was $7.5\pm1\%$. MDI group included 73 patients and the CSII group 58 patients (> 6 months, mean time of 3.8 ± 2.6 years). At diagnosis, most were at Tanner Stage I on both groups (38 vs 46). Height SD at diagnosis was similar (0.18 ± 1.16 vs 0.17 ± 1, $P=0.91$). HbA1c was lower in the CSII group ($7.7\%\pm1.2$ vs $7.3\%\pm0.68$ $P=0.02$) as well as MPTH SD (-0.67 ± 0.8 vs -0.3 ± 0.9, $P=0.005$). Mean height SD at age 18 was not different between groups (-0.21 ± 0.98 vs -0.13 ± 0.96, $P=0.98$). One patient had short stature without pathological cause. DifSD was lower in the CSII group (0.5 ± 0.9 vs 0.17 ± 0.9, $P=0.02$) and was associated with age at diagnosis and duration of DM1. There was no association between DifSD and pubertal Tanner stage at diagnosis, HbA1c and the presence of other autoimmune diseases.

Conclusions

The height SD at 18 years was comparable with the population without DM1. Despite the limitations of HbA1c in assessing glycemic control, it was lower in the CSII group. Even though MPTH has been reached regardless of the treatment, the difSDS in the group with CSII was lower, suggesting further fulfillment of growth potential.

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RC1.6

Developing a diabetes management system integrated with salivary glucose sensors

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Background and objectives

Diabetes is estimated to affect more than half a billion people worldwide, of which approximately 9.5 million live in Turkey. Currently, glucoSemeasurements are made with invasive techniques (eg finger puncture or interstitial glucose sensors) that can negatively affect monitoring. In addition, since glucose results cannot be seen by physicians/nurses in real time, treatment decisions are delayed and diabetes control becomes difficult. As a group of researchers from the fields of medicine, engineering and informatics, we aimed to develop a non-invasive saliva glucose sensor and an integrated diabetes management system

Materials and methods
We developed disposable nanoelectromechanical (NEMS) biosensors, electronic equipments (potentiostat) and a software for integrated monitoring of diabetes.
Results
First, the triple electrode structure was coated with ZnO nanorods and glucose oxidase. After the biosensor properties were characterized, the produced sensor structure was packaged and made ready for clinical use. Sensor calibration and performance tests were performed in saliva with multiple tests. Using artificial saliva, It was shown that substances such as vitamin C, paracetamol, etc. in the environment did not cause interference in glucoSemeasurement. A lag time of approximately 10 minutes was found between the salivary glucose and capillary blood glucoSemeasurements (ie, the zero-minute salivary glucose level was found to be highly correlated with the capillary blood glucose level 10 minutes ago; r = 0.986, $P < 0.001$).
Conclusion
Within the scope of this project, we have developed a prototype system includes low-cost, disposable biosensors and a software to facilitate integrated diabetes management. Easy-to-implement and low cost such systems will increase patient comfort in diabetes management, improve quality of life and facilitate follow-up.
Keywords:
Diabetes Mellitus, Noninvasive Glucose Monitoring System, Salivary Glucose, Biosensor
Sponsor:
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Rapid Communications 2: Thyroid

RC2.1

Increased risk of Graves' orbitopathy following Covid-19 vaccination
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Background
Vaccination is a widely adopted measure against the severe-acute-respiratory-syndrome-coronavirus-2 (SARS-CoV-2) causing Covid-19 pandemic. Both SARS-CoV-2 infection and Covid-19 vaccines have been associated with several thyroid disorders. We studied the risk of Graves' orbitopathy (GO) following Covid-19 vaccination.
Methods
The study included 98 consecutive patients (71 females and 27 males, mean-age 50 years) attending our tertiary referral centre for new-onset ($n = 90$) or reactivation ($n = 8$) of GO occurred in the period Jan 2021 – Aug 2022, immediately following the extensive Covid-19 vaccination campaign launched in late 2020. GO was associated to Graves' disease in 91 (93%), euthyroidism in 5 (5%) and Hashimoto's thyroiditis in 2 (2%) patients. Family history for thyroid/autoimmune disorders was positive in 54 (55%) patients. We used a self-controlled-case-series study design, validated in assessing vaccine safety. For each vaccinated patient, we calculated person-days in time-windows after each dose, defined as "exposed" if GO onset/reactivation occurred 1-30 days after vaccination and "unexposed" if occurring outside such time-window. Poisson regression models were fitted to calculate incidence rate ratio (IRR) and 95% confidence-intervals (CI) of exposed vs unexposed. Sensitivity analyses were conducted considering only new-onset GO, gender, age, smoking, Covid-19 vaccine type and number of doses.
Results
Covid-19 vaccines were administered in 81 (83%) and never in 13 (13%) patients; data were missing in 4 patients. Of the 81 vaccinated subjects, 25 (31%) developed GO 1-30 days after vaccination (exposed) and 56 (69%) outside such time-window (unexposed). The overall IRR for GO was 3.12 (CI 1.94-5.02) and as high as 5.10 (CI 2.61-9.93) in patients below 50 years of age. Gender, smoking, Covid-19 vaccine type and number of doses did not significantly impact on the overall IRR, also when restricting the analysis to cases of new disease onset only. The GO severity was similar across the study subgroups. SARS-CoV-2 infection occurred in 23/98 (23%) patients during the study period and seemed not associated with GO.
Conclusions
This study shows a 3-fold increased risk of either developing or reactivating GO shortly after Covid-19 vaccination, rising-up to 5-fold in subjects of less than 50 years of age. Possible mechanisms involve the interaction of the spike protein with the widely expressed ACE-II receptor, cross-reactivity of the spike with thyroid self-proteins or immune reactions induced by adjuvants. Until more safety data about Covid-19 vaccines will be available, caution and strict monitoring of individuals undergoing vaccination is suggested, especially if young and prone to develop thyroid autoimmunity.
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RC2.2

Overtreatment of differentiated thyroid cancer: impact on real world clinical practice of conservative guidelines, as recorded by the Italian Thyroid Cancer Observatory Study
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On behalf of Italian Thyroid Cancer Observatory, Italy

Background
The incidence of differentiated thyroid cancers is increasing, mainly due to the overdiagnosis of small papillary thyroid cancers (less than 1 cm, previously known as microcarcinomas). There is a broad consensus in reducing the surgery extent and the use of radioiodine treatment in low-risk cases by most recent clinical practice guidelines focusing on thyroid cancer treatment. The adoption in real clinical practice is usually slow. The aim of this study is to estimate the changes in real clinical practice, using prospective, observational data of the Italian Thyroid Cancer Observatory (ITCO) study.
Methods
The web-based ITCO database was started in 2013 and now includes prospectively collected data on more than 12 000 patients with confirmed diagnosis of thyroid cancer, from 51 different clinical centers. Data about initial treatment and follow-up clinical assessment are prospectively collected by the treating physicians, according to their usual clinical practice. The study is registered at ClinicalTrials.gov (NCT04031339). For the purposes of this evaluation, we grouped the cases according to the year of the initial treatment: group 1 (2013-2015) and group 2 (2016-2020). We then calculated the rate of patients treated with lobectomy and the rates of patients not submitted to radioiodine ablation, according to their risk of persistent/recurrent disease, as estimated by the system proposed by the 2015 ATA Guidelines for differentiated thyroid cancer.
Results
The final cohorts included 6873 patients. The rates of lobectomies (without completion thyroidectomy) increased from 1.7% to 6.9% ($P < 0.001$) in patients with low risk of persistent or recurrent disease according to the ATA Guidelines, and from 0.6% to 2.3% for intermediate-risk patients ($P = 0{,}004$). About the radioiodine treatment, its use is decreased from 41.7 to 30.6% in low-risk patients ($P < 0.001$); and from 87.8% to 74.5% in intermediate-risk patients ($P < 0.001$). In all risk classes, the avoidance of radioiodine treatment did not impact the short-term outcomes (as estimated by the 1-year response to treatment, evaluated according to the suggestions of the ATA Guidelines).
Conclusions
For patients with low- or intermediate-risk thyroid cancer, real-world clinical application of practice guidelines is progressively recorded, even if the overall adherence is still low and there is ample room for improvement.
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RC2.3

A simplified four-tier classification of thyroid core needle biopsies (CNB) is an efficient system. Evidence based on more than 1,000 surgical cases
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CNB is increasingly being used as a diagnostic test for thyroid nodules with an inadequate (Bethesda 1) or indeterminate (Bethesda 3 and 4) FNAC results, which can account for up to 30% of the samples in some studies. CNB, using larger specimens and histological sections rather than cytological samples, allows better definition. We propose a simplified four-tiered classification of CNB specimens instead of the Bethesda system and evaluate its efficiency compared to definitive surgical diagnosis. CNB samples were classified as inadequate, benign, follicular tumor (FT) or malignant. The last two were considered neoplastic surgical indications. Follicular tumors included samples with numerous follicles, usually

microfollicles, with scant colloid and insufficient nuclear changes to be considered a follicular variant of papillary thyroid cancer (FV-PTC). Thyroidectomy was recommended for benign biopsies based on clinical sings, patient preference, or goiter growth. Inadequate samples were usually biopsied again. The final results of the last CNB were compared with the histological results of surgery. CNBs were collected since 2005, when we adopted it as main diagnostic test because our poor FNAC results. A total of 1,687 thyroid nodules were operated on in 1,506 patients out of more than 6,000 CNBs from 2005 to 2022: 23 with inadequate CNB, 865 with benign CNB, 294 diagnosed as follicular tumors in CNB (94 oxyphilic) and 505 as malignant (478 PTC). Inadequate CNBs revealed 18 benign lesions and five malignancies. three with other biopsied nodules with surgical indication in the same gland. Of the 865 benign CNBs, 820 were benign nodules and 45 were neoplastic, 26 were follicular adenomas and 19 were malignant (16 PTC and three follicular carcinomas). Follicular tumors were 39 benign nodules (13.3%) and 253 neoplastic: 215 follicular adenomas (73.1%) and 40 malignant (13.6%): 19 PTCs, ten FTCs, nine HCCs, one MTC and one invasive parathyroid carcinoma. Malignant CNBs were confirmed in 493/505 nodules. Eleven were hyperplastic and one was an oxyphilic adenoma. The overall sensitivity of malignant CNB was 96.3%. The specificity of benign CNB was 98.7%. The positive predictive value of malignant CNB was 97.6% and the negative predictive value of benign CNB was 94.8%. Only 17.4% of the operations were due to an indeterminate biopsy (FT) and only 13.6% of these were malignant, although 79.9% corresponded to neoplastic lesions, more of which were adenomas. CNB confirmed as a very reliable diagnostic technique, with high diagnostic efficiency of the proposed four-tiered classification.

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RC2.4

Cell free DNA Integrity index to differentiate benign from malignant thyroid nodules

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Introduction
Cell-free DNA (cfDNA) integrity in plasma has been investigated as a non-invasive marker in cancer. Thyroid cancer the most common endocrine malignancy sometimes presents as indeterminate nodules and difficult to diagnose without histopathology.
Aim of the study
The present study aims to test the hypothesis that the presence of longer DNA strands circulating in plasma can be considered a marker for thyroid cancer.
Methods
Patients presenting with thyroid nodules underwent ultrasonography with Thyroid Image Reporting and Data Systems (TIRADS) scoring and FNAC (Bethesda classification). All patients in Bethesda 3,4,5,6 underwent surgery and histopathological confirmation. Patients in Bethesda 2 (cosmetic concerns, compressive symptoms) underwent surgery, rest were presumed benign on the basis of USG, FNAC features and clinical follow-up. Cell-free DNA was extracted from plasma and quantified. We adopted a quantitative real-time PCR (qPCR) approach based on the quantification of two amplicons of different length (67 and 180 bp respectively) to evaluate the integrity index 180/67 for APP gene. The genomic DNA isolated from the MDA-T32 papillary thyroid cancer cell line was used as reference to determine the relative DNA strand integrity because culture cells contained highly intact genomic DNA. The Ct value of the 180 bp for a sample was subtracted from that for the MDA-T32 control to obtain a (ΔCt) value for 180 bp. Likewise, the Ct value of a 67 bp for the sample was subtracted from that for the MDA-T32 control to obtain a (ΔCt) value for 67 bp. CfDNA Integrity index was calculated by ratio of ΔCt180/ΔCt 67 bp.
Results
A total of 131 subjects were recruited, of these 72 were benign and 59 had differentiated thyroid cancer proven by histopathology. CfDNA integrity index was higher in differentiated thyroid carcinoma patients (median 0.45, 95% CI: 0.36-0.52) than in subjects with benign nodules (median 0.32, 95% CI: 0.27-0.39). The cell free DNA integrity index 180/67 was significantly higher in malignant nodules compared and benign nodules ($P=0.001$).
Conclusions
CfDNA integrity index 180/67 could be a parameter for monitoring cfDNA fragmentation in thyroid cancer patients and a promising marker in the diagnosis of thyroid nodules that warrants further validation in future prospective trials.

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RC2.5

Lack of GPER-TSHR heteromers is a hallmark of thyroid cancer

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Thyroid cancer is the most common type of endocrine tumor and reaches the peak of incidence between the age of twenty and fifty years. It has 4-fold higher prevalence in females than males, suggesting that estrogens and their receptors could be involved in thyroid cancer pathogenesis. Previous studies demonstrated allosteric interference operated by G protein-coupled estrogen receptor (GPER) to molecules structurally similar to the thyroid-stimulating hormone (TSH) receptor (TSHR). We hypothesize that G protein-coupled estrogen receptor (GPER) may interact with TSHR, differently modulating proliferative signals in healthy *versus* cancer thyroid cells. Mechanistic experiments evaluating TSHR/GPER heteromers and signaling were performed on papillary thyroid carcinoma (K1), follicular thyroid epithelial (Nthy-ori 3-1) and COS7 (control) cell lines, and confirmed in papillary, follicular, and anaplastic tumors *versus* healthy primary thyroid tissues by immunofluorescence (IF) and proximity ligation assay (PLA). Cell lines were co-transfected with specific plasmids to evaluate effects on the TSH-induced activation of Gαs and Gq protein-associated transduction pathways, under TSHR/GPER co-expression. Cell lines were treated with 300 nM TSH and 730 pM estradiol. Intracellular levels of cAMP and calcium ion (Ca^{2+}) increase were measured by bioluminescence resonance energy transfer (BRET), while IP1 by homogeneous time resolved fluorescence (HTRF). Results were compared by Kruskall-Wallis test ($n=6$; $P<0.05$) and corrected by Dunn's post-hoc test. We found TSHR/GPER co-expression and physical interaction in healthy thyroid follicles using two different methods (IF and PLA), and confirmed these results in cell lines by BRET. Surprisingly, no GPER expression was found in histological sections of papillary, follicular and anaplastic thyroid cancer, as confirmed by the absence of IF signal and heteromers. In TSHR expressing cell lines, TSH activated Gαq-mediated signals, i.e. IP1 ($n=6$; $P<0.05$) and Ca^{2+} ($n=3$; $P<0.05$), and cell proliferation, while it was not under TSHR/GPER co-expression. Control experiments with Gq and PLC inhibitors, i.e. YM-254890 and U73122, confirmed GPER-like inhibition of TSH-induced IP1 production. Instead, the presence of GPER unaffected TSH/GαS-mediated cAMP production ($n=6$; $p\geq0.05$). Cell treatment with estradiol and GPER antagonist (5 μM; G15) had no effects ($n=6$; $p\geq0.05$), revealing that GPER inhibits TSHR/Gq regardless of ligands. GPER/TSHR heteromers drive potentially protective effects in thyroid cells, while the lack of GPER unlock TSH/Gq-dependent proliferative intracellular pathways in tumor cells. This data suggests that lack of GPER may be related to thyroid tumor pathogenesis.

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RC2.6

Abstract withdrawn

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Rapid Communications 3: Pituitary and Neuroendocrinology 1

RC3.1

Abstract withdrawn

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RC3.2

Increased intracellular and extracellular myocardial mass on cardiac magnetic resonance imaging in patients with acromegaly

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Background
Acromegaly is associated with an increased left ventricular mass, as reported in echo-based and more recently in few cardiac MRI studies. One possible explanation of this increased ventricular mass could be water retention and consequently edema of the ventricular wall.
Methods
In this prospective, cross-sectional study 26 patients with active acromegaly and 31 control subjects of comparable age and sex were investigated by cardiac MRI. Patients were explored before and after GH/IGF-I lowering treatment. Cardiac morphology, function and myocardial tissue characteristics were assessed. T2 times were used as a reflect of intramyocardial water content.
Results
Ventricular mass (58.1 (54.7; 68.6) vs 46.0 (41.3; 49.8) g/m^2; $P<0.001$) and volume (97.3 (88; 101.2) vs 81.6 (78.0; 96.2) ml/m^2; $P=0.0069$) were higher in patients compared to controls, without affecting cardiac function. T2 times were not increased in active acromegaly. Both, intracellular (87.9 (71.2; 103.6) vs 67.2 (51.6; 76.9) g/m^2; $P<0.001$) and extracellular (31.9 (26.1; 36.6) vs 21.8 (19.2;24.7) g/m^2; $P<0.001$) myocardial mass were higher in patients compared to controls. GH, but not IGF-I strongly correlated with myocardial mass ($r=0.756$; $P<0.001$). In multiple regression analysis, in addition to male sex and HDL cholesterol, the presence of acromegaly was an independent predictor of total myocardial mass and extracellular mass, whereas systolic arterial blood pressure predicted intracellular mass. GH/IGF-I lowering treatment reduced intracellular mass and ventricular volume, without affecting other myocardial tissue characteristics.
Discussion
Acromegaly results in a disease specific form of myocardial hypertrophy, characterized by an increase in intra- and extracellular mass, which is reversed after GH/IGF-I lowering treatment. This increase in ventricular mass is different to previous observations in essential hypertension. No differences in T2 times suggest against myocardial water retention in active acromegaly as explication of increased extracellular mass.

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RC3.3

The spectrum of cardiac disease in patients with acromegaly: results from the SUM trial

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Introduction
Cardiac abnormalities are common in patients with acromegaly and contribute to the increased morbidity and mortality of the disease. Cardiac magnetic resonance (CMR) is the established, non-invasive gold standard for measuring morpho-functional changes of the heart. We aimed to detect cardiac alterations in patients with acromegaly through CMR and to identify potential risk factors associated with cardiac impairment.
Materials and methods
This is a prospective case-control study. Consecutive patients with acromegaly, screened in the SUM study (EudraCT number: 2015-004498-34), either cured or with active disease, entered the study and were compared with a sex, age, and BMI-matched control group. Metabolic, clinical, and CMR parameters were assessed and compared between groups. Parametric and non-parametric tests were performed, as appropriate.
Results
Twenty patients with acromegaly (7 females, mean age 48 years; 13 males, mean age 50 years) and 17 controls were included. No significant differences were observed in the prevalence of cardiometabolic comorbidities, including dyslipidemia, glucoSe-metabolism impairment, hypertension, and obesity, between patients and controls. CMR parameters were indexed to body surface area. Left ventricular-end-diastolic volume (LV-EDVi) and LV-end-systolic volume (LV-ESVi) were higher in patients with acromegaly than in controls ($P<0.001$), as were left ventricular mass (LVMi) ($P=0.001$) and LV-stroke volume (LV-SVi) ($P=0.028$). Right-ventricle (RV) EDVi and ESVi were higher, whereas RV-ejection fraction (RV-EF) was lower ($P=0.002$) in patients with acromegaly than in controls ($P<0.001$). None of the patients had LV hypertrophy according to conventional CMR thresholds. IGF-1 levels directly correlated with cardiac CMR parameters: LV-EDVi ($r=0.47$; $P=0.037$), LVMi ($r=0.45$; $P=0.044$), and LV-SVi ($r=0.500$, $P=0.025$). Indeed, a subgroup analysis in patients with biochemically uncontrolled disease ($n=3$) showed higher LV-EDVi ($P=0.034$), LV-SVi ($P=0.033$), LVMi ($P=0.002$) and RV-SVi ($P=0.044$) compared to cured ($n=6$) and controlled patients ($n=11$). No differences were found when data were stratified according to the presence or absence of the main cardiometabolic comorbidities. Lastly, after adjusting cardiac parameters for the normal population age and sex reference ranges, as well as physiological sex-related differences, male acromegalics showed higher LVMi ($P=0.025$) and interventricular septum thickness ($P=0.003$) than females.
Conclusions
Our results confirm CMR as a useful tool for the diagnosis of acromegalic cardiomyopathy: a cluster of biventricular structural and functional impairment, resembling the dilated cardiac phenotype, which likely results from specific pathways triggered by GH-IGF-1 excess. Interestingly, sex-related differences advocate a possible interaction of sexual hormones in cardiac disease progression, but further studies are needed to confirm these findings.

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RC3.4

SGLT2 Inhibitors in a case series of diabetic acromegaly patients: Effects beyond diabetes

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Objective
There has been no consensus on the medical management of diabetes in acromegaly patients. The primary approach is like the general population, and metformin is considered first-line therapy. Sodium-glucose cotransporter inhibitors (SGLT2is) are a novel antidiabetic class which has an improving effect on insulin resistance. There is no recommendation regarding their use for diabetic acromegaly patients despite their potential beneficial effects by inducing glucosuria, osmatic diuresis, and cardiovascular safety. Euglycemic diabetic ketoacidosis might constitute a barrier related to insulin deficiency since GH per se increases lipid oxidation and ketone bodies. A recent pilot study showed the ability of an adjuvant Eucaloric very-low-carbohydrate ketogenic diet controlled IGF-I levels in patients with acromegaly whose disease was uncontrolled with first-generation somatostatin receptor ligand therapy[1]. Thus, we aimed to evaluate the outcomes of SGLT2is on diabetes control, also control of IGF-1 levels in a subset of acromegaly patients.

Table 1 Anthropometric and biochemical parameters of patients at basal and 3. month

	Weight (kg)		Glucose (mg/dl)		GH (μg/l)		IGF-1(μg/l)		HbA1c (%)		Creatinine (mg/dl)	
month	0	3	0	3	0	3	0	3	0	3	0	3
Mean	92.63	90.42	106.83	105.50	1.41	1.32	224.03	200.30	6.65	6.18	0.90	0.98

Methods
We conducted a proof-of-concept study involving 6 patients (3 women, 3 men) to investigate whether a 3-month, SGLT2 is as adjuvant treatment to metformin (if not contraindicated) would affect IGF-I concentrations besides glucose parameters in patients with uncontrolled acromegaly. The treatment of acromegaly remained stable during the intervention.
Results
We showed a decrease in mean glucose, Hemoglobin A1C (HbA1c), and insulin-like growth factor 1 (IGF-1) levels. Body weight also showed a pattern of decline. Although blood ketone levels did not increase, serum creatinine levels showed an increasing trend. We had to withdraw a patient do the increased creatinine level (Table 1).
Conclusion
İt is noteworthy that a patient-tailored approach should be initiated not only for managing acromegaly and diabetes separately but also for combining therapies to enhance the effects. Although SGLT-2 inhibitors seem to have favorable effects on acromegaly patients, a caution on renal functions should be considered. Far-reaching studies are needed to evaluate the utility and adverse effects of this unique antidiabetic class in acromegaly patients.
Reference
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RC3.5

The Reassessment of Therapeutic Decisions by Clinicians According to the SAGIT® Instrument in Acromegaly: Results of a Multicenter Study

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Objective
SAGIT, a new instrument designed for therapeutic decision, is not routinely used yet. While the medical treatment was mostly planned according to disease activity by hormonal evaluation, the therapeutic decision has tried to be standardized with the SAGIT instrument. The aim of this study is to reassess the therapeutic decisions by clinicians in the management of acromegaly according to the SAGIT instrument.
Material and Method
This multicenter, retrospective study was conducted at twelve experienced centers from our country and included patients with acromegaly who needed medical treatment, primary or post-surgery. Characteristics of patients and the components of SAGIT:(S) signs/symptoms, (A) associated comorbidities, (G) growth hormone (GH) levels, (I) insulin-like growth factor-1 (IGF1) level, and (T) tumor features were recorded at baseline, before and 3,6, and 12 months after medical treatment. The relationship between SAGIT scores and therapeutic decisions was evaluated.
Results
Of 322 (175 females/147 males) patients enrolled, 38 patients received primary medical treatment, whereas 284 patients received post-surgical medical treatment. A SAGIT score of 6 was significantly detected as the optimal cutoff for an evaluation of acromegaly disease activity based on hormonal control only with GH and IGF1 levels at each visit. The clinician's therapeutic decisions at every visit were assessed according to the cutoff level of SAGIT score for disease activity (Table 1). In patients with the uncontrolled disease according to the SAGIT score at the 3rd and 6th months visits and whoSemedical treatment was unchanged, a significant decrease in SAGIT score both between the 3rd and 6th, and 6th and 12th months were found ($P=0.002$, $P<0.001$, respectively). However, it was revealed that adequate disease control could not be achieved as the SAGIT scores remained at 6 and above for both the 6th and 12th months visits.
Conclusion
If clinicians had changed therapeutic decisions according to the SAGIT criteria, more than 50% of patients would have required treatment intensification for the patients found to be uncontrolled according to the optimal cutoff SAGIT score of 6, also shown in the validation studies. As a result, the SAGIT scores of these patients remained equal to or above the cutoff point during the 12-month follow-up. This result showed that the SAGIT instrument should be emphasized more strongly to achieve individualized treatment.

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Table 1.

		Medical Treatment Dose Modification		
		Unchanged	Increased	Decreased
SAGIT 3rd month scores($n=238$)(n,%)	<6	59(89.4)	6(9.1)	1(1.5)
	≥6	63(36.6)	99(57.6)	10(5.8)
SAGIT 6th month scores($n=198$)(n,%)	<6	57(79.2)	12(16.7)	3(4.2)
	≥6	55(43.7)	67(53.2)	4(3.2)
SAGIT 12th month scores($n=221$)(n,%)	<6	73(81.1)	7(7.8)	10(11.1)
	≥6	59(45)	69(52.7)	3(2.3)

RC3.6

Discontinuation of long-term growth hormone treatment in adults with severe growth hormone deficiency: A United Kingdom web-based survey of endocrine practice

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Introduction
In adults, treatment of growth hormone deficiency (GHD) with daily recombinant human growth hormone (GH) injections has shown to improve many clinical features associated with GHD. Currently, many adults with GHD receive GH indefinitely, even when they fail to report any obvious benefits from this treatment. Additionally, evidence on the impact of discontinuing long-term GH therapy is limited. We conducted a survey of UK endocrine clinicians (doctors and specialist nurses) between 01/06/2022 and 31/08/2022 to understand the current practice of offering GH treatment discontinuation in adults with GHD.
Methods
A web-based multiple-choice questionnaire was developed and administrated by an online platform Survey Monkey®. The survey was distributed to the UK Society for Endocrinology membership. It consisted of 15 questions with sections on demographics, number of adult patients treated with GH, number of adult patients on GH replacement therapy for more than 5 years and the current practice/criteria used by the clinicians when offering a period of GH treatment discontinuation.

Results
102 endocrine clinicians completed the survey, majority of which were from England ($n=91$, 89%). Of the 102 participants, 65 (33 endocrinologists and 32 specialist nurses) indicated active involvement in managing adult patients with GHD. Amongst the 65 respondents, 27.7% ($n=18$) were routinely offering a period of GH discontinuation to patients who have been on treatment for a long time. However, only 6% ($n=4$) confirmed that that a clinical guideline/protocol was in use to guide the practice of GH treatment discontinuation in adults. 29.2% of clinicians ($n=19$) supported that GH treatment discontinuation should be routinely offered to adult patients with GHD on long-term treatment and a further 60% ($n=39$) would consider treatment discontinuation for long-term users of GH treatment whilst 9.2% ($n=6$) indicated discontinuation should not be offered. At post-discontinuation review, majority of clinicians would complete IGF-1 level measurement (84.6%, $n=55$), quality of life assessment by AGHD questionnaire (89.2%, $n=58$) and signs and symptoms assessment (75.4%, $n=49$).
Conclusions
This first survey of GH treatment discontinuation practice in the UK highlights areas of uncertainty amongst endocrine clinicians regarding the appropriateness of offering GH treatment discontinuation in adults with GHD who have been on long-term therapy. Although a significant number of clinicians consider GH treatment discontinuation could be routinely offered to adult patients, this survey highlights the need for research to assess the effects of GH treatment discontinuation in adults, to guide the development of evidence-based recommendations to inform clinical practice.

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Rapid Communications 4: Reproductive and Developmental Endocrinology

RC4.1

Sars-CoV-2 infection leads to significant and long-lasting changes in women's reproductive health

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Background
Reproductive health is a state of complete physical, mental, and social well-being. So far, there is limited evidence about the consequences of Sars-CoV-2 infection on women's reproductive health.
Aim
To determine the effects of Sars-CoV-2 infection on women's reproductive health.
Methods
We created an anonymous survey about reproductive health and shared it with women of reproductive age between May 2022 and December 2022. All women used their menstrual cycle (MC) diary while filling out the survey. Surveys were stratified into two groups based on RT-PCR/Antigen test results: positive (CP) or negative (CN). All reported changes in CP referred to time after the Sars-CoV-2 infection and in CN to a pandemic period in general.
Results
704 women completed the survey. Based on inclusion, exclusion, and complete data availability 461 surveys were taken into the final analysis: 129/28% CN-mean age 28.8 ± 9.7, mean BMI 22.5 ± 4.1 kg/m^2 and 332/72% CP, mean age 28.3 ± 8.7, mean BMI 22.3 ± 3.7 kg/m^2. There was no difference in age or BMI between the groups ($p>0.05$). 303/65.7% reported being vaccinated. When compared to CN, 253/54.8% CP reported changes in MC ($P<0.001$); 94/20.3% CP reported shortening of MC length ($P=0.001$) with a mean shortening of 3.3 days, as well as more pronounced premenstrual syndrome symptoms (PMS) ($P<0.001$); 83/18% CP reported heavier menstrual bleeding (HMB) ($P<0.001$); 64/13.8% CP reported more painful menstrual bleeding (MB) ($P=0.017$); 45/9.76% reported prolonged MB duration ($P=0.026$); 32/6.9% CP reported a dyad consisting of shortening of MC length, and HMB ($P=0.003$); 258/55.9% CP reported that the changes in their MC are still present ($P=0.005$) with an average duration of 290 days. Age, BMI nor vaccination did not affect changes in MC ($p>0.05$). In fact, vaccination had a protective effect against MC changes, which was close to statistical significance ($P=0.087$, $B=-0.542$, OR 0.582; 95% CI=0.312-1.083). Regarding mental health when compared to CN surveys, 116/25.1% CP reported having low mood ($P=0.036$); 89/19.3% CP reported poor sleep ($P=0.017$); 24/5.2% CP surveys reported excessive alcohol use ($P=0.006$). Mental health changes did not affect changes in MC ($p>0.05$). In CP group, the duration of Sars-CoV-2 infection was the most significant predictor of changes in MC ($P=0.009$, $B=0.070$, OR 1.072; 95% CI=1.02-1.13).
Conclusions
Sars-CoV-2 infection leads to long-lasting changes in women's reproductive health. Possible consequences are yet to be elucidated as the most remarkable change was the shortening of MC length which is an important clinical predictor of reproductive axis aging and lower fertility rate.

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RC4.2

Evolution of cardiovascular risk markers in polycystic ovary syndrome: Results from a long-term monocentric cohort study

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Background
Many questions concerning polycystic ovary syndrome (PCOS) remain unsolved, such as the long term evolution of cardiovascular (CV) risk markers and the risk for CV events.
Methods
A total of 119 PCOS patients diagnosed in 2009 by NIH criteria at our Unit were evaluated at baseline for cardiovascular risk markers (hypertension, diabetes mellitus-DM, dyslipidaemia, obesity, carotid intima media thickness-cIMT, and epicardial fat thickness-EFT) and cardiovascular events. All subjects were subsequently reevaluated between 2020 and 2021.
Results
Participants mean age was 39.9 ± 7.6 years at baseline and 51.9 ± 7.6 years at the end of the study, with a prevalence of menopausal state of 6.1% and 39.3%, respectively. At baseline, no major or minor CV events were detected, but 2 cases of angina pectoris (1.7%), 1 case of transient ischaemic attack (0.8%), 3 cases of arterial revascularization (2.5%), and 1 case of cardiac insufficiency (0.8%) were documented at the end of the study. Prevalence of hypertension, type 2 DM, dyslipidaemia, and obesity were initially 27.2%, 12.2%, 59.0% and 32.1%, and 44.4%, 18.6%, 87.2% and 47.2% at final reevaluation ($P<0.001$, $P=0.065$, $P<0.001$, $P<0.05$ vs baseline, respectively). cIMT was significantly increased at final examination (0.58 ± 0.16 mm vs 0.81 ± 0.27 mm, $P<0.001$), and the% of patients with cIMT$\geq$ 1 mm or with carotid plaques passed from 1% to 26.4% ($P<0.001$). In contrast, a significant decrease in EFT was detected from baseline to the end of the study (0.86 ± 0.35cm and 0.41 ± 0.23cm, $P<0.001$).
Conclusions
This cohort study shows that PCOS is indeed characterized by a high prevalence of cardiovascular risk markers, with a tendency to increase over time; nonetheless, not all cardiovascular risk markers worsen steadily, with some interesting beneficial variations occuring in the late reproductive or early post-menopausal years.

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RC4.3

Body composition and metabolic characteristics in different PCOS phenotypes

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Introduction
Polycystic ovary syndrome (PCOS) is the most prevalent endocrinopathy among women during reproductive age. Using ESHRE/ASRM diagnosis of PCOS is considered when 2 of 3 criteria are present: polycystic ovary morphology (PCOM), oligo/anovulation (ANOV) and hyperandrogenism (HA). These criteria form four different phenotypes: A (ANOV, HA, PCOM), B (ANOV, HA), C (HA, PCOM) and D (ANOV, PCOM). Several studies have found differences in anthropometric, hormonal and metabolic characteristics between PCOS phenotypes. Among the non-insulin-derived indices, the single-point insulin sensitivity estimator (SPISE) index showed better accuracy than other indicators in the prediction of metabolic syndrome. The aim of this study was to analyze anthropometric and metabolic characteristics in different PCOS phenotypes and compared to control group.
Subjects and methods
We analyzed 307 women with PCOS divided into four phenotypes groups PCOS-A ($n=126$, age 25.63 ± 4.6 years, BMI 24.97 ± 6.2 kg/m^2), PCOS-B ($n=40$, age 26.13 ± 6.4 years, BMI 28.33 ± 7.3 kg/m^2), PCOS-C ($n=83$, age 26.06 ± 5.6 years, BMI 24.91 ± 5.4 kg/m^2) and PCOS-D ($n=58$, age 25.26 ± 4.6 years, BMI 21.09 ± 3.1 kg/m^2) and 87 women in control group (age 29.25 ± 5.8, BMI 23.33 ± 6.1 kg/m^2). Body composition was analyzed using bioimpedance. Lipid indices, basal glucose and insulin were measured, while HOMA-IR and SPISE index were calculated.
Results
Compared to control group only women with PCOS-B had higher BMI, waist circumference (WC), body fat mass, body and trunk fat percentage ($P<0.001$, $P<0.001$, $P=0.001$, $P=0.002$, $P=0.008$, respectively), while same characteristics were higher in phenotypes PCOS-A, B and C in comparison to PCOS-D phenotype. Women with PCOS-B had more body fat mass and higher WC compared to PCOS-A group. Both control group and all patient with PCOS showed similar HOMA-IR and basal insulin levels, but SPISE index was statistically lower in PCOS-B group compared to controls and in PCOS A, B and C group compared to PCOS-D group, as well in PCOS-A than in PCOS-B group. SPISE index showed strong negative correlation in all phenotype groups with body and trunk fat mass, body and trunk fat percentage, total body water, BMI and WC and negative correlation with HOMA-IR in PCOS-A, B and C group ($r=-0.368$, $P<0.001$, $r=-0.433$, $P=0.013$, $r=-0.405$, $P<0.001$, respectively).
Conclusion
Not all patient with PCOS have same cardiometabolic risk factors. PCOS-B phenotype showed most prominent metabolic risk factor profile. SPISE index seems to represent accurate risk marker in more metabolic weighted PCOS-A and PCOS-B. The assessment of different risk factors in PCOS phenotypes could be used for prediction of long-term metabolic outcomes.

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RC4.4

Is AMH a regulator of autophagy in the ovary?

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Background
The reserve pool of primordial follicles (PMF) is finely regulated by molecules implicated in follicular growth or PMF survival. Anti-Müllerian Hormone (AMH), produced by granulosa cells of growing follicles, is known for its inhibitory role in the initiation of PMF growth. We observed in a recent *in vivo* study that injection of AMH into mice seemed to induce an activation of autophagy, a cytoplasmic lysosomal-dependent degradation system, which is important for starvation adaptation and cellular quality control. Furthermore, we observed an activation of the transcription factor FOXO3a by AMH, which is also known to regulate autophagy. Many studies highlighted the key role of autophagy in the ovary at different stages of folliculogenesis and particularly in PMF survival. The objective of our study was to understand how AMH stimulates autophagy and in particular what is the role of the transcription factor FOXO3a which is involved in the maintenance of PMF in quiescence but also in the regulation of autophagy.
Methods
We used an *in vitro* approach on organotypic cultures of prepubertal mouse ovaries, treated or not with AMH. Autophagy was monitored by immunofluorescence and western-blot analysis of LC3, a specific marker of autophagosomes. The phosphorylation status of FOXO3a was analyzed by Western blot. The expression of genes involved in autophagy was quantified by RT-qPCR.
Results
We showed that autophagosome biosynthesis and autophagic flux are increased in AMH-treated ovaries. AMH also induces a FOXO3a dephosphorylation which is translocated to the nucleus where it exerts its transcriptional activity. We observed that the transcription of FOXO3a target genes involved in autophagy (*Atg16l1*, *Gabarapl2*, *Wipi2*, *Atg2a*, *Ulk1*, *Zfyve1*, *Atg5*) is significantly increased in AMH treated ovaries.
Discussion
This *in vitro* approach shows that AMH is able to stimulate autophagy in mouse ovaries by increasing the expression of a number of FOXO3a target genes involved in this process. This is a completely new role for this hormone which protects the pool of primordial follicles by inhibiting their growth but also by inducing autophagy to allow them to survive.

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RC4.5

Women carrying CYP21A2 mutations display clinical findings and metabolic/hormonal profile analogous to women with non classical congenital adrenal hyperplasia and polycystic ovary syndrome

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Heterozygotes carrying CYP21A2 gene mutations are found in 5-10% of the general population in Mediterranean countries. Accumulating data suggest a survival advantage of this population, despite the fact that carriers of two mutations suffer from either classical or non-classical congenital adrenal hyperplasia (NC-CAH), an entity with increased mortality. In an attempt to elaborate on this issue we evaluated females of reproductive age with CYP21A2 heterozygocity (HET). We have analyzed data from 56 HET were compared with 105 controls, 64 untreated females suffering from NC-CAH and 63 women with Polycystic ovary syndrome (PCOS), of similar age and BMI. We have found that the prevalence of hirsutism (54 vs 8%) and acne (44 vs 4%) was higher in HET than controls and the degree of menstrual irregularities was similar between HET and NC-CAH and worse than controls. The lipidemic profile was significantly better in HET compared to PCOS (Cholesterol 170.20 ± 37.06 vs 187.67 ± 39.34 mg/dl, HDL 61.42 ± 26.11 vs 46.81 ± 8.58 mg/dl). However, Testosterone 0.78 ± 0.45 vs 0.50 ± 0.25 ng/dl), SHBG (38.20 ± 20.11 vs 56.20 ± 31.37 nmol/l), FAI (9.56 ± 3.45 vs 5.37 ± 1.24) and DHEAS concentrations (2.62 ± 1.31 vs 1.27 ± 0.94 nmol/l) were comparable among HET, NC-CAH, PCOS and significantly higher than controls, as well as insulin (13.88 ± 7.96 vs 7.51 ± 2.82 IU/l) and HOMA-IR (2.95 ± 1.60 vs 1.65 ± 0.67). Androstenedione (5.97 ± 2.88 vs 8.80 ± 3.45 ng/ ml) and 17hydroxy-progesterone (4.32 ± 2.02 vs 13.75 ± 8.34 ng/ ml) values were lower than the corresponding ones in NC-CAH, but significantly higher in HET than PCOS and controls. Finally, ovarian Pcomorphology prevalence was found similar in HET to NC-CAH and PCOS. Therefore, we conclude that women pf reproductive age carrying CYP21A2 mutations display a favorable lipidemic profile, but a similar degree of hyperandrogenic signs, menstrual disturbances, insulin resistance, hyperandrogenemia and ovarian morphology with women suffering from either PCOS or NC-CAH. Therefore, it is obvious that these women, when identified they should be carefully followed up.

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RC4.6

Bone and sexual health in adult women with complete androgen insensivity syndrome: A single centre experience

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Background
Low bone mineral density (BMD) and reduced sexual satisfaction have been reported in complete androgen insensitivity syndrome (CAIS). Nevertheless, conclusive data on the prevalence and on the optimal management of these conditions are still lacking.
Aims
To assess bone and sexual health in adult women with CAIS with and without gonadectomy.
Methods
Single-centre, prospective study of 27 adult CAIS (age 35.2±8.7 years), 22 patients with gonadectomy (age 13.4±7.1 years) and 5 with intact gonads. All patients with gonadectomy were on hormonal replacement therapy (HRT) (median age of start 16 years, range 12.5-19.5 years). Two patients were on testosterone therapy while all the others on estradiol (8 transdermal and 12 on oral formulation). Adherence to HRT was assessed through self-reporting and it was intermittent in two patients. The primary outcome was the evaluation of bone health, as measured with dual-energy x-ray absorptiometry and morphometric vertebral fractures. Secondary outcomes were sexual function, as measured with the Female Sexual Function Index (FSFI) and Female Sexual Distress Scale-Revised (FSDS-R) and body uneasiness, as measured with the Body Uneasiness Test (BUT).
Results
in all patients, BMD Z-score was reduced at lumbar spine (LBMD-Z -1.66±0.88) and at the hip (THBMD-Z -0.4±0.8). In particular, LBMD-Z and THBMD-Z was −1.4±0.64 and 0.04±0.62 in patients with intact gonads and −1.7±0.9 and -0.5±0.8 in patients with gonadectomy, respectively. LBMD-Z was <-2 in 2 patients with intact gonads and in 8 patients with gonadectomy. No fractures were recorded in any patient. FSFI, FSDS-R and BUT tests were collected in 20 patients. Eleven patients (4 with intact gonads) showed a sexual dysfunction at FSFI (score <26,55). Interestingly, in the group with intact gonads, 3 of 4 patients with sexual dysfunction had testosterone levels below normal range. When considering FSDS-R, 12 patients (2 with intact gonads) showed a hypoactive sexual desire disorder (HSDD) (score >11). Similarly, 9 patients (2 with intact gonads) reported body uneasiness at BUT (Global Severity Index >1.2).
Conclusions
Our results confirm the reduction of BMD in CAIS with and without gonadectomy. Moreover, sexual dysfunction, HSDD and body uneasiness is common. Preservation of gonads not always guarantees optimal hormone levels and gonadectomy must be considered after spontaneous pubertal development. The lack of defined guidelines on the most appropriate management of CAIS, reinforces the need to perform further investigations, in order to establish an adequate treatment, thus guaranteeing an improvement quality of life and reducing the risk of complications.

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Rapid Communications 5: Adrenal and Cardiovascular Endocrinology 1

RC5.1

Abstract withdrawn

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RC5.2

Analysis of germline mutations in patients with non-syndromic adrenocortical carcinoma

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Background
Adrenocortical carcinoma (ACC) is a rare cancer associated with hereditary syndromes in 10% of cases. However, data on germline variants (GVs) in adult patients with sporadic ACC are limited.
Methods
We analyzed germline DNA from 150 adult patients with sporadic ACC sequentially referred to our centers between 1998-2019. We designed a custom panel of 17 genes potentially involved in the pathogenesis of ACC: AIP, APC, ARMC5, ARNT, BRCA1, BRCA2, CTNNB1, IGF2, MEN1, MSH2, MSH6, PDE8B, PDE11A, PRKACA, PRKACB, PRKAR1A, and TP53. NGS data were analyzed by a semi-automated bioinformatic pipeline. All GVs were studied using effect predictor tools (PolyPhen and SIFT). Specific databases (ClinVar, Varsome, gnomAD, IARC TP53, HGMD) were used for variant classification according to ACMG criteria. Variants interpreted as pathogenic (P) or likely pathogenic (LP) were considered as positive. Clinical, pathological and genomic data were analyzed in different Cox models to study prognostic impact of covariates for disease-free survival (DFS), progression-free survival (PFS) and overall survival (OS).
Results
We identified 21 unique GVs in in 9 genes including APC ($n=3$), ARMC5 ($n=3$), MSH2 ($n=3$), PDE11A ($n=3$), TP53 ($n=3$), MSH6 ($n=2$), PDE8B ($n=2$), AIP ($n=1$) and CTNNB1 ($n=1$). Eleven positive GVs were found in 14/150 patients (9.3%). We found a new GV in TP53 (G105D) in a patient who was later found to have a sister with ACC and, for the first time, 3 GVs in ARMC5 (P731R). Patients with ARMC5 GVs had large cortisol-secreting tumors and one case displayed combined pathologic features of ACC and macronodular cortical disease. Positive GVs were associated with a shorter OS (50 vs 142 months, HR 1.81; 95% CI, 0.86-3.82, $P=0.118$) and PFS (8 vs 30 months, HR 3.11; 95% CI, 1.57-6.16, $P=0.001$) but not DFS (27 vs 32 months, HR 1.07; 95%CI, 0.52-2.22, $P=0.845$). At multivariate analysis, known clinical factors (age, surgery of primary ACC, ENSAT stage, hypercortisolism) were found to have prognostic impact on OS. However, GVs remained independent predictors of PFS and OS in metastatic patients.
Conclusions
In a series of 150 patients with ACC, we found that 9.3% of them had positive GVs. We describe for the first time the presence of ARMC5 GVs in patients with ACC and we found a novel pathogenic variant of TP53. Pathologic features of one ARMC5 case suggest a possible progression from macronodular adrenal hyperplasia to ACC. Finally, the present findings suggest that GVs can affect ACC progression and survival of affected patients.

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RC5.3

Study of somatic molecular heterogeneity in bilateral macronodular adrenocortical disease (BMAD) by NGS panel in a cohort of 26 patients

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Introduction
Bilateral macronodular adrenal disease (BMAD) is a genetically heterogeneous disease that can be caused by *ARMC5* or *KDM1A* alterations. Indeed, a germline and somatic event leading to a bi-allelic inactivation of *ARMC5* or *KDM1A* are responsible for 20 and 1% of BMAD cases, respectively. Genetic analysis identified three molecular groups: *ARMC5*, *KDM1A* and no genetic cause known to date. Although there is a high heterogeneity in the somatic events identified in the different nodules from *ARMC5* mutated patients, the somatic events were never studied on several nodules from *KDM1A* mutated patients. The aim of this work was to study the mutational profile of different nodules from the same patient in a cohort of BMAD to describe the somatic alterations of patients with pathologic germline *ARMC5* or *KDM1A* variants and to look for potential pure somatic genetic alterations in patients with no known genetic cause.
Patients and methods
26 patients underwent surgery for BMAD at the Cochin Hospital between 2006 and 2021. 148 DNA samples were extracted from formalin-fixed and paraffin-

embedded material after macrodissection. Qualified DNA were sequenced by Illumina NGS sequencing for a panel of 7 genes: *ARMC5*, *GNAS*, *KDM1A*, *PDE8B*, *PDE11A*, *PRKACA* and *PRKAR1A*.
Results
For 3 patients all DNA samples ($n=23$) were too degraded to be analyzed. Out of the 7 patients with a germline pathological *ARMC5* variant, 6 had 2 to 8 pathological somatic *ARMC5* variants for 3 to 10 nodules sampled. The last patient had one unique somatic event detected on 5 nodules. Out of the 3 patients with a germline pathological *KDM1A* variant, each nodule had a loss of heterozygosity. Out of the 13 patients without a pathological *ARMC5* or *KDM1A* variant, no genetic alterations were found. In patients for whom a germline pathological variant was known, we detected a somatic event in 56 of the 61 nodules sampled (92%).
Discussion
Our study is the first to explore the mutational profile of different nodules from the same patient isolated by macrodissection on a series of BMAD and the first to study this profile in patients with bi-allelic *KDM1A* inactivation. We confirm the heterogeneity of *ARMC5* secondary events and show a high homogeneity of *KDM1A* alterations. In patients without germline alteration no somatic alterations were found suggesting that the molecular mechanisms in these patients remain to be discovered.

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RC5.4

Primary bilateral macronodular adrenal hyperplasia (PBMAH) is likely a genome instability disease due to ARMC5's role in resolving transcription-replication conflict

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ARMC5 mutations are associated with PBMAH risks, but the ARMC5 action mechanism remains unknown. We discovered that ARMC5 was part of a novel ubiquitin ligase (E3) specific for RPB1, the largest Pol II subunit. ARMC5 deletion significantly reduced RPB1 ubiquitination and increased RPB1 accumulation. Surprisingly, the degradation of not only RPB1 but all the 12 subunits of Pol II was compromised in the absence of ARMC5, suggesting that this E3 acts on RPB1 and molecules in its vicinity, and ARMC5 mutation causes an enlarged Pol II pool. The stalled Pol II due to DNA damage needs to be removed by degradation via the ubiquitin/proteasome system, or else the transcription machinery will suffer from a genome-wide jam and transcription decrease. However, a combined analysis of RPB1 ChIP-seq and RNA-seq of the ARMC5 KO adrenals revealed that a lack of this major Pol II-specific E3 did not lead to a generalized transcription decrease. This suggests that either under physiological conditions, Pol II stalling is not common, or there is a so-far unknown mechanism to recycle the stalled Pol II. Although ARMC5 mutations are associated with adrenal hyperplasia, the proliferation of most types of KO cells was reduced. This raises an intriguing possibility that the physiological function of the E3 is to remove Pol II from the DNA track to resolve the transcription-replication conflict. Failure to do so in the S phase will slow down replication accompanied by genome instability, which is a pro-oncogenic condition. The enlarged Pol II pool in the KO adrenals led to differential expression of 1486 genes. The majority of these genes were upregulated, and some of the upregulated ones were oncogenes. The expression of StAR, the rate-limiting enzyme in cortisol biogenesis, was reduced, probably as a secondary effect of the enlarged Pol II pool; this decrease explains the reduced cortisol secretion per cell in PBMAH. ARMC5 was previously incorrectly called a tumor suppressor gene. We now know that it affects more upstream processes controlling the general replication and transcription. Based on our findings, we propose the following model. The defective ARMC5-containing E3 leads to an enlarged Pol II pool and compromises transcription-replication conflict resolution. The former upregulates some oncogenes. The latter causes oncogenic genome instability and, at the same time, reduced replication. The sum effect of all these conflicting forces is the pathogenesis of slow-growing tumors or hyperplasia such as PBMAH.

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RC5.5

Clinical relevance of targeted sequencing in paraffin-embedded samples for prognostic classification of adrenocortical carcinoma

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Adrenocortical carcinoma (ACC) is a rare malignant tumour with heterogeneous outcome. Prognostic classification relies on individual clinical/histopathological parameters that have limited performance. Recent studies proposed the use of selected DNA-based biomarkers to improve prognostication of ACC. Aim of the study was to perform a comparative analysis of DNA-based biomarkers (BM) for prognostic assessment of ACC by evaluating their added value to the established prognostic S-GRAS score, a combination of five clinical/histopathological parameters. A total of 194 formalin-fixed, paraffin-embedded (FFPE) samples from patients with histologically confirmed ACC were analysed. Targeted DNA sequencing and pyrosequencing were used to detect single nucleotide variations (SNV) in ACC-specific genes (two different panels with 100 and 33 genes, respectively) and methylation in the promoter region of *PAX5*. ENSAT tumour stage, age, symptoms, resection status, and Ki-67 index were collected for calculation of the S-GRAS score. Endpoints were overall survival (OS), progression-free survival (PFS), and disease-free survival (DFS). Prognostic role of each parameter was evaluated by uni- and multivariable Cox regression analysis and compared by Harrell's C-index. The prognostic role of following DNA-based BMs was confirmed at univariable analysis: more than one SNV-affected gene (BM1), alterations in Wnt/β-catenin and Rb/p53 pathways (BM2) and hypermethylated *PAX5* (BM3) ($P<0.01$ for both OS and PFS). However, only BM2 and BM3 showed an independent prognostic impact at multivariable analysis including S-GRAS score ($P<0.05$ for all three endpoints, HR between 1.4 and 1.9). Importantly, looking at the C-index, the best discriminant prognostic model was represented by the combination of DNA-based BM2 and BM3 with S-GRAS (combined score) as compared to S-GRAS alone, which was the second best prognostic factor (C-index for OS 0.734 vs 0.704, for PFS 0.697 vs 0.676, for DFS 0.674 vs 0.633, respectively). In conclusion, targeted DNA-based biomarkers evaluated on routinely available FFPE samples improve prognostication of ACC beyond combined clinical/histopathological parameters. This approach is easily applicable in clinical practice and may help to optimise patient's management.

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RC5.6

IGF2R: a new player in the insulin-like growth factor 2 (IGF2) pathway sustaining adrenocortical carcinoma cells growth

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Adrenocortical carcinomas (ACC) are rare endocrine tumors that originate in the cortex of the adrenal gland. They are characterized by the overexpression of insulin-like growth factor 2 (IGF2), whose bond with two tyrosine-kinase receptors, IGF1R and IR, activates a cancer-promoting signalling cascade. Another component of the IGF system is mannose 6-phosphate/insulin-like growth factor 2 receptor (IGF2R), a scavenger receptor able to bind specifically IGF2. Its main role is to internalise IGF2 and direct it to lysosomal degradation,

suggesting an anti-oncogenic role. However, the study of its involvement in different tumors has highlighted a diverse role, even making it a marker of poor prognosis. Aim of the present study was to deepen the knowledge on IGF2R role in ACC investigating its expression levels, involvement in the proliferative mechanism and interaction with the other receptors of the IGF2 pathway. IGF2R expression was evaluated in two human ACC cell lines (MUC-1 and H295R), 7 ACC tissue samples, and 7 normal adrenal tissues (NA). Our results showed that ACC tissues and cell lines had increased IGF2R protein levels compared to NA ($P<0.01$). To investigate IGF2R role in cell proliferation we altered its expression in MUC-1 and H295R cell lines. We demonstrated that IGF2R genetic silencing reduced cell proliferation (-11.65±8.73% $P<0.01$ in MUC-1; -14.02±12.35% $P<0.01$ in H295R). Similarly, IGF2R-neutralizing antibody incubation exerted anti-mitotic effects (-16.85±2.57% $P<0.05$ in MUC-1). On the opposite, IGF2R transient transfection promoted cell growth (+14.84± 12.54% $P<0.01$ in MUC-1; +24.49±15.62% $P<0.001$ in H295R). To investigate the molecular mechanism involved, we tested the effect of IGF2R manipulations on the expression of the other receptors of the IGF2 pathway. MUC-1 silenced for IGF2R showed a significant decrease in IGF1R protein expression (-35 ±37% $P<0.05$); accordingly, after IGF2R transfection, IGF1R protein level was increased (+20±6% $P<0.001$). In conclusion, IGF2R is involved in the mechanisms driving cell proliferation in ACC, possibly relating also to the alteration of IGF1R expression. Since its upregulation in ACC and its pro-mitotic action, IGF2R may represent a promising therapeutic target for the treatment of ACC.

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Rapid Communications 6: Endocrine-related Cancer

RC6.1

Aberrant activation of Wnt/β-Catenin signaling pathway drives the expression of poor prognosis-associated microRNAs in adrenocortical cancer

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Adrenocortical carcinoma (ACC) is a rare malignancy with dismal prognosis. Deregulated microRNA (miRNA) expression has been implicated in ACC aggressiveness. Nevertheless, the mechanisms underlying such deregulations remain unknown. Aberrant Wnt/β-Catenin signaling has been reported in about 40% of ACC and is associated with poor outcome. In the present work, we aimed to investigate the link between constitutive activation of Wnt/β-Catenin pathway and miRNA expression alterations in ACC. To this end, we used inducible shRNA-mediated gene silencing of β-Catenin (β-Cat) in ACC cells. The miRnome of ACC cells was analyzed using RNA-Sequencing. Selected miRNAs and mRNAs were validated using quantitative PCR and functional experiments. Prognostic values of Wnt/β-Catenin pathway components or mutational status and their correlations with miRNA/mRNA expressions were determined in COMETE-ENSAT and TCGA cohorts. We carried out the first miRnome analysis in β-Catenin-deficient (β-Cat-) ACC cells. Twelve upregulated miRNAs and 42 downregulated miRNAs among which miR-139-5p and miRNAs of the 14q32 locus were identified in β-Cat- cells. Downregulation of selected poor prognosis-associated miRNAs was confirmed using RT-qPCR. Remarkably, the expression of the intronic miR-139-5p was decreased by 90% in β-Cat- cells with a concomitant repression of its host gene phosphodiesterase 2A and upregulation of its target gene N-Myc Downstream-Regulated Gene 4 (NDRG4). In ACC patients, miR-139-5p levels were highly correlated with the levels of PDE2A and anti-correlated with those of NDRG4. MiR-139-5p and PDE2A expressions were higher in patients with mutations in components of Wnt/β-Catenin signaling pathway or high expression of LEF1, with LEF1 proving a better predictor of prognosis than Wnt/β-Catenin signaling pathway mutational status. These findings suggest that in addition to inducing protein-coding target genes in ACC, constitutively active Wnt/β-Catenin signaling upregulates the expression of a subset of miRNAs involved in tumour aggressiveness and poor clinical outcome.

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RC6.2

Refocusing on somatostatin receptors as clinical targets in pheochromocytomas and paragangliomas

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Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine neoplasms (NENs) that arise in the adrenal medulla and paraganglia, respectively. As occurs in the rest of NENs, PPGLs commonly present a high density of somatostatin receptors (SSTs) on their membrane. However, unlike in most NENs, somatostatin analogues (SSAs) do not represent a suitable therapeutic target in PPGLs, and the mechanisms underlying this mismatch are still unclear. In this study, we aim to identify the molecular elements and processes involved in the lack of response of PPGL to SSAs, with the ultimate goal of sensitizing PPGL to these drugs. To this end, we first explored by RNA-seq analysis two cohorts of 204 and 95 samples, and the TCGA dataset, focusing on determining the profile of SSTs in PPGL samples and the differences in their expression depending on driver genes mutations. Then, in vitro assays were performed using two cell lines representative of the pathology: rat PC-12 cells and human SK-N-AS cells (wildtype and *SDHB*-KD). We determined their response to somatostatin, cortistatin, SSAs (octreotide and pasireotide) and specific SSTs agonists on different functional assays, including cell proliferation, colony formation and wound healing, as well as key intracellular signaling pathways. Transcriptomic analyses revealed a marked difference in the expression pattern of SSTs between the different PPGL molecular clusters, with a clear divergence in the type of SSTs expressed across the mutated driver genes. In striking contrast, we did not observe any antitumor effect in response to somatostatin, cortistatin or SSAs in vitro. Interestingly, however, the use of selective agonists for each SST revealed antiproliferative effects in human cells, specifically in those lacking *SDHB*, whereas, no significant effects were observed on colony formation and migration assays. Current analyses are focused on the elements downstream SST signaling. Taken together, our results suggest previously unrecognized molecular associations between the SST system and PPGL subtypes and invite to further explore the underlying mechanisms behind their lack of response to SSA therapy.

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RC6.3

Efficacy and safety of temozolomide in the treatment of aggressive pituitary neuroendocrine tumours in Spain

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Introduction
Current guidelines propose temozolomide (TMZ) as the first-line chemotherapy for aggressive pituitary neuroendocrine tumors (PitNETs), but no clinical trials have been conducted and clinical experience in this context is limited.
Patients and methods
A retrospective study of patients with aggressive pitNETs treated with TMZ was conducted by the members of the Neuroendocrinology Working Area of the Spanish Society of Endocrinology and Nutrition.
Results
Twenty-eight patients (9 women and 19 men), aged 46.6 + 16.9, from 10 Spanish Neuroendocrinology Units were included. Visual disturbances were present in 82.1%, headache in 71.4% and hypopituitarism in 67.9%. Four patients had Cushing's disease (one of them Nelson's syndrome), 9 prolactinomas and 15 clinically non-functioning pituitary adenomas (NFPAs). Among the 15 NFPA, immunohistochemistry was positive for ACTH in 7 cases, for GH in 3 cases, for prolactin in one case, for gonadotrophins in one case, and 3 tumors were negative for all pituitary hormones. Median size at diagnosis was 10.5 cm^3 (IQR 4.7-22.5), with cavernous invasion in 88% and no metastases. Pre-TMZ treatment, these data were 5.2 cm^3 (IQR 1.9-12.3), 89.3% and 14.3% (2 intracranial and 2 spinal metastases). Before TMZ treatment all patients had undergone surgery (1-5 surgeries, median 2), 25 (89.3%) had received radiotherapy (7 of them reirradiated) and 13 (46.4%) had received cabergoline. One patient interrupted TMZ prematurely due to intercurrent complications. The other 27 patients received a median of 13 cycles (range 3-66) of TMZ with a median final daily dose of 300 mg (IQR 200-334). Eight patients (29.6%) had a significant reduction (>30%) in tumor volume and 14 (51.9%) attained tumor stabilization. After a median follow-up of 29 months (IR 10-55), 8 out of those 22 progressed (median time from treatment to progression 16.5 months, RI 7-27). Four patients received a new course of TMZ treatment. Seven patients (25%) died (all of them because of tumor progression or complications of treatments) at 77 months (IQR 42-136) from diagnosis and 29 months (IQR 16-55) from TMZ first treatment. Adverse effects occurred in 18 patients (14 mild and 4 moderate or severe).
Conclusions
TMZ is an effective medical treatment for aggressive pitNET (81.5% tumor shrinkage or stabilization) but is sometimes followed by tumor progression. Its safety profile is acceptable. After a median follow-up of 29 months, we observed a 25% mortality.

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RC6.4

Much more than hormonal resistance: estrogen receptor activating mutations mediate chemotherapy resistance in breast cancer

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Resistance to endocrine treatment develops with time in virtually all patients with metastatic breast cancer (BC), and eventually most of them are treated with chemotheray. Our group and others discovered a group of mutations in the ligand binding domain (LBD) of the estrogen receptor (ER), that are the direct cause of resistance in ~40% of the patients. The most common mutations are Y537S and D538G ER. Clinical data indicate an association between those ER mutations worse prognosis. The aim of this study was to study the role of ER mutations in promoting (i) resistance to chemotherapy; (ii) identify mechanisms mediating chemo-resistance. We studied chemo-resistance, using viability, colony formation and apoptosis assays, in MCF7 BC cells stabely expressing the WT-ER or Y537S and D538G ER mutations (mut-ER). The results showed that mut-ER cells exhibit elevated resistance to paclitaxel and doxorubicin. Nest, we studied the expression of the MDR1 gene, that encodes an ATP pump that is associated with chemoresistance. We observed increased expression of MDR1 mRNA and protein in mut-ER cells. Furthermore, we observed activation of the JNK pathway in mut-ER cells as evidanced by increased JNK and cjun phosphorylation, as well as cjun transcriptional activity. Our next goal was to find out whether cjun regulates MDR1 expression in mut-ER cells. Indeed, chromatin immunoprecipitation assay showed that cjun bound MDR1 promoter. Inhibition of JNK using SP600125 decreased MDR1 expression and also restored sensitivity to chemotherapy. Moreover, immunohistochemical studies of mut-ER tumors in mice, showed higher expression of MDR1 and cjun compared to WT-ER tumors. Finally, we analyzed duration of response to chemotherapy among 51 breast cancer patients with endocrine resistance, of which mut-ER was detected in 20 patients, whereas 31 had WT-ER. The analysis showed a significant shorter duration of chemotherapy treatment among patients with mut-ER, indicative of refractory response. In conclusion, ER activating mutations are associated with resistance to chemotherapy, mediated by the cjun-MDR1 axis. Our studies suggest novel, non-endocrine, therapeutic approaches aimed at targeting chemoresistance.

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RC6.5

The frequency of differentiated thyroid carcinoma recurrence in retrospective analysis of 3087 consecutive patients

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Introduction
An increase in the incidence of differentiated thyroid cancer (DTC) has been observed in recent decades. Despite the excellent prognosis, DTC patients remain on lifelong oncologic follow-up after treatment, due to fear of recurrence.
Aim
Was to evaluate the frequency of real recurrence, defined as appearance of structural or biochemical disease after >12 month period of no evidence of disease (NED) in DTC patients.
Material and methods
A retrospective analysis of medical records of 3087 consecutive DTC patients (after the operation alone or operation and 131-I therapy) being under observation from 1998 to 2021. Clinicopathological features including histology, tumor size, extrathyroidal extension, angioinvasion, multifocality, resection margin involvement, lymph node (LN) and distant metastases, were obtained from all the patients. Moreover, the stage of the disease was assessed or reassessed according to TNM 8th edition of UICC and response to therapy according to the ATA recommendation, in all the patients. Only patients with an excellent response were submitted to further analysis. The percentage of recurrence and cumulative recurrence rate (CRR) were analyzed.
Results
Females accounted for 85.4% of the patients. Papillary TC was the most common in 2827 patients (91.6%). Median age was 52 years (range: 13-86 years). Median tumour size- 9 mm (range 0-144 mm). 15% of the patients had LN and 2.7% distant metastases. Excellent response to therapy was observed in 2302 patients (74.6%)- among them true recurrence developed in 34 patients (1.5%). The recurrence was significantly more common in patients with: other than PTC type of TC ($P=0.009$), larger tumour size ($P<0.0001$), angioinvasion ($P=0.0015$) and lymph node metastases ($P=0.0063$), TNM stage ($P=0.0013$) and treated with 131-I ($P=0.0045$). In the univariate analysis, histological type-PDTC (HR: 9.581 CI:2.278-40.293 P=0.002), tumour size 11-40 mm (HR:2.703 CI:1.291-5.662 $P=0.008$) and >40 mm (HR: 6.879 CI:2.423-19.533 $P<0.001$), LN metastases (HR: 3,861 CI:1.752-8.511 $P<0,001$), angioinvasion (HR: 4.836 CI: 1.186 – 10.698 $P<0.001$), stage II TNM (HR: 5.4945 CI:2.389 – 12.636 $P<0.001$) were associated with a risk of recurrence. Higher CRR was observed in poorly differentiated and oncocytic TC, than in FTC and PTC.
Conclusion
1. Real recurrence is rare in patients with DTC- it accounts for 1,5%.
2. Despite of excellent response to the therapy, patients with advanced stage of disease have higher risk of recurrence.

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RC6.6

C-peptide level concomitant with hypoglycemia gives better performances than insulin for the diagnosis of endogenous hyperinsulinism: a monocentric study of 159 fasting trials

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Introduction
The gold standard for insulinoma diagnosis is still 72-hours fasting trial with the aim to trigger Whipple's triad. In this context, biological diagnosis of endogenous

hyperinsulinism relies on the occurrence of a hypoglycemia, concomitant with inadequate high insulin and C-peptide levels. However, diagnostic cut-offs are not consensual among the different learned societies (*Endocrine Society 2009, NANETS 2010, ENETS 2012*). The objective of this work was thus to propose optimized cut-offs for these three parameters for the diagnosis of endogenous hyperinsulinism.

Methods

All the patients having performed a fasting trial in Cochin Hospital Endocrinology Department between February 2012 and August 2022 were included. The results of glycemia, insulin and C-peptide levels during fasting trial were collected and analyzed.

Results

One hundred and fifty-nine patients were included: 26 with endogenous hyperinsulinism and 133 without endogenous hyperinsulinism. ROC analysis of glycemia nadir during fasting trial identified the value of 2.3 mmol/l as the optimal cut-off, ensuring a sensitivity of 100% associated with a specificity of 81%. The median time to glycemia nadir was 22.5 (min 8 – max 66.5) hours in the group of patients with endogenous hyperinsulinism in comparison to a median of 62.5 (min 24 – max 84) hours in the group of hypoglycemic controls. ROC analysis of insulin and C-peptide levels concomitant with hypoglycemia $<$ 2.3 mmol/l showed very good diagnostic performances of both parameters with respective cut-offs of 3.1 mUI/l (sensitivity = 96%; specificity = 92%) and 0.30 nmol/l (sensitivity = 96%; specificity = 100%). Insulin to glycemia ratio as well as C-peptide to glycemia ratio (in pmol/mmol) at the time of glycemia nadir did not show better diagnostic performances than C-peptide alone.

Conclusion

A C-peptide level 0.3 nmol/l concomitant with a hypoglycemia $<$ 2.3 mmol/l appears as the best criterion to make the diagnosis of endogenous hyperinsulinism. Insulin level can be underestimated on hemolyzed blood samples, frequently observed in fasting trial, and thus shows lower diagnostic performances.

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Rapid Communications 7: Pituitary and Neuroendocrinology 2

RC7.1

Splicing factor 3B subunit 1 (SF3B1) role in PRL-secreting PitNETs

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Dopamine receptor type 2 (DRD2) represents the main target for pharmacological therapy with dopamine agonists (DAs) in PRL-secreting neuroendocrine pituitary tumors (PRL-PitNET), even if about 10% of patients is resistant. A single paper recently described a somatic mutation in the gene encoding splicing factor 3B subunit 1 (SF3B1) in about 20% of patients with PRL-PitNET, that was associated with PRL hypersecretion, increased cell proliferation and invasion and reduced progression free survival. SF3B1 is a key component of pre-mRNA processing, crucial for splicing machinery assembly. Aims of the study were: 1) to characterize the genetic profile of PRL-PitNET, searching for somatic mutations in SF3B1^{R625H} hotspot region; 2) to test in tumoral lactotroph cells the effects of SF3B1 inhibitor pladienolide-B and the role of SF3B1 in affecting DRD2 agonist cabergoline antitumoral effects. SF3B1^{R625H} hot-spot region has been sequenced in PRL-PitNET tissues and rat PRL-secreting pituitary tumoral cells mmQ. SF3B1 was inhibited with pladienolide-B or silenced by siRNA technique, and cells have been analysed to measure cell proliferation, apoptosis, secretion and cell cycle markers activation. No mutation in SF3B1 gene was found in our cohort of PRL-PitNET ($n = 40$), nor in rat lactotroph mmQ cells. Pladienolide-B 50 nM treatment strongly reduced cell proliferation (-92 $\pm$ 5%, $P < 0.001$) and increased apoptosis (+10-fold, $P < 0.001$) in mmQ, and similar results were found in primary PRL-PitNET cultured cells, wild-type for SF3B1. Moreover, pladienolide-B reduced PRL secretion in primary cells (-45 $\pm$ 6.5%, $P < 0.001$). SF3B1 silencing in mmQ cells abolished cabergoline inhibitory effects on cell proliferation (-22 $\pm$ 4.8%, $P < 0.001$), AKT phosphorylation (-31 $\pm$ 24.6%, $P < 0.01$), cyclin D3 (-23 $\pm$ 7.6%, $P < 0.05$) and increase of p27 levels (+20 $\pm$ 8.6%, $P < 0.05$). In addition, SF3B1 knock down was associated with DRD2 reduction (-66.4 $\pm$ 8% of DRD2 transcript, $P < 0.05$, and -51 $\pm$ 13.2% of DRD2 protein, $P < 0.001$), and the same effects were observed after pladienolide-B incubation. On the other hand, cabergoline reduced SF3B1 protein expression levels in mmQ (-60 $\pm$ 40%, $P < 0.05$) and in 2 PRL-PitNET (-43 $\pm$ 6.1%, $P < 0.01$). Our data did not confirm the presence of SF3B1^{R625H} mutations in a multicentre cohort of PRL-PitNET. In contrast, we observed that SF3B1 seems to play a relevant role in tumoral lactotroph cells. Indeed, SF3B1 inhibitor pladienolide-B exerted antiproliferative, proapoptotic and antisecretory effects in PRL-PitNET cells wild-type for SF3B1. Moreover, SF3B1 is required for expression and signalling of DRD2.

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RC7.2

Transcription factor analysis for pituitary tumours: Are results always consistent and reliable?

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Background

Improved diagnostic precision is achieved with the addition of transcription factor (TF) analysis to characterise pituitary tumours. Clinicopathological studies have demonstrated a reduction in the prevalence of true null cell tumours (NC) and a rise in plurihormonal (PH) tumours, in comparison to methods based on hormone staining. There remains a high degree of heterogeneity in epidemiological and clinical patterns seen in studies. We hypothesise that variations in methodological and diagnostic criteria contribute to inconsistencies observed. We therefore reviewed methodological approaches to pituitary tumour diagnosis in recent studies.

Methods

A PubMed search was conducted with keywords "pituitary tumour" (and variations in nomenclature), "classification", "transcription factor" and "clinicopathological". Abstracts of studies involving pituitary tumours, published in English between 2015 to February 2023 were screened for relevance. Studies were excluded if they did not assess for presence or absence of all 3 TF or if analyses were limited to tumour subsets only. Case reports and review articles were excluded. Remaining studies were evaluated for their methodology, type of antibody and scoring strategy. Outcomes were number of NC and PH tumours.

Results

Of the 13 studies included in this review, 9 were conducted retrospectively using stored tissue blocks. Threshold definitions for positive identification of tumour types varied from 5% tumour cells positive to 80%. Mean storage time of oldest specimens used in retrospective studies was 17.1 $\pm$ 6.8 years at time of publication. There was a positive linear correlation between number of tumours classified as NC and the age of tissue used for analysis ($R^2 = 0.71$, $P = 0.03$). Five studies with clinical data reported that 33-100% of NC tumours showed radiological invasion. In the non-functioning tumour category, the percentage of individual tumour subtypes varied substantially across all studies: 6.9 $\pm$ 4.7% silent PIT1, 17.4 $\pm$ 7.9% silent corticotroph tumours, 67.1 $\pm$ 10.1% gonadotroph tumours, 5.5 $\pm$ 4.5% NC tumours and 3.2 $\pm$ 3.0% silent PH tumours. Studies that used a cut-off of 5% or 10% tumour cells to define TF positivity were able to diagnose PH tumours. When a high cut-off of 80% was applied, PH tumours were not identified.

Conclusion

Higher proportion of NC tumour classification is seen with older tumour specimens, possibly representing false negative staining. Positivity cut-off influences the ability to detect PH tumours. We highlight the need for large prospective studies and a standardised approach to assessment of transcription factor expression before developing guidelines for clinical management based on TF analysis.

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RC7.3

AZP-3813, a bicyclic, 16-amino acid peptide antagonist of the human growth hormone receptor, effectively suppresses IGF1 in beagle dogs

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Medical treatment of acromegaly is based on either suppressing pituitary growth hormone (GH) secretion or by inhibiting GH action by preventing interaction with its receptor in order to suppress the elevated levels of insulin-like growth factor 1 (IGF1). AZP-3813 is a 16-amino acid, bicyclic peptide antagonist of the GH receptor (GHR) with K_D of 1.9 nM for the human GHR. Previously, AZP-3813 was demonstrated to suppress IGF1 secretion in juvenile rats in a dose-related manner, and to maintain IGF1 suppression when given daily for extended periods. To examine the ability of AZP-3813 treatment to suppress IGF1 levels in normal dogs, we injected adult, non-fasted, male Beagle dogs subcutaneously with AZP-3813 at doses of 0.1, 1 or 10 mg/kg. Three dogs received a single 0.1 mg/kg dose of AZP-3813 and, after 7 days, the same dogs received a single 10 mg/kg dose of AZP-3813. A second group of three dogs received 1 mg/kg AZP-3813 daily for 5 days. Blood was collected 3 days and immediately before treatment, and at 15 min, 30 min, and 1, 2, 4, 8, 24, 48, 72 and 96 hours after the single injections of 0.1 and 10 mg/kg AZP-3813, and after the first and fifth injections for dogs receiving 1 mg/kg AZP-3813 daily for five days. Pre- and 24 hour post-injection samples were assayed for total IGF1 content by radioimmunoassay, and all samples were analyzed for AZP-3813 content by LC-MS/MS. Maximal blood concentrations (C_{max}) of AZP-3813 were observed 4 hours following injection, and were 0.72 ± 0.028, 7.2 ± 0.36 and 58.9 ± 2.8 mg/ml for the 0.1, 1 and 10 mg/kg doses, respectively. After the fifth injection of 1 mg/kg, blood levels of AZP-3813 were 8.7 ± 0.34 mg/ml, indicating compound accumulation. Elimination curves for all doses were parallel with a half-life of 14.2 ± 0.47 hours. While the 0.1 mg/kg dose of AZP-3813 was ineffective (-2.2 ± 7.1% decrease from baseline), 24 hours after injection of 1 and 10 mg/kg AZP-3813, IGF1 levels were suppressed by 21.4 ± 2.7% and 27.8 ± 1.5%, respectively. The repeated injection of 1 mg/kg AZP-3813 maintained a similar magnitude of IGF1 suppression through 72 hours following the fifth injection, while suppression of IGF1 was maintained at a similar level through 72 hours after the single injection of 10 mg/kg. These results demonstrate that the potent GHR antagonist activity of AZP-3813 translates to a sustained suppression of IGF1 in normal dogs and further support the development of AZP-3813 as a potential therapy for acromegaly.

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RC7.4

Effects of prolactin excess and treatment with cabergoline on bone mineral density and fracture risk in men

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Purpose

The present study aims to investigate the effects of hyperprolactinemia (HPRL) and its pharmacological control with Cabergoline (CAB) on the risk of fractures in male patients affected by prolactinoma.

Methods

Observational single-center study was conducted on 39 male patients (median age $49 \pm 12,4$ y) with prolactinoma, including 37 with macroprolactinoma and 2 with empty sellae. In patients PRL levels at diagnosis (PRL 0'), PRL at evaluation (PRL 1'), treatment duration (TD), CAB cumulative (CD) and mean dose (CM) were calculated. In the whole study population ($n=39$), anthropometric parameters (weight, height, BMI), testosterone dose, metabolic (vitamin D, serum calcium, fasting glucose, HbA1c), hormonal (FSH, LH, parathormone, total testosterone) parameters were evaluated. BMD was assessed by means of lumbar (LTS) and femoral neck t-scores (FTS), derived from bone mineralometry. Comparison of numerical data between patient groups stratified by quartiles of age, BMI, testosterone levels, PRL 0', PRL 1' and CM was detected.

Results

Based on the age quartiles, a statistically significant difference was found in the BMI between the four groups ($P=0.03$), particularly between the I and II groups ($P=0.022$). While no statistically significant differences in other parameters were found between the four groups. Based on testosterone quartiles, a statistically significant difference was found in PRL 1' ($P=0.018$), particularly between group I and group II ($P=0.017$). Furthermore, no statistically significant differences were found in the groups of patients divided into quartiles of BMI, PRL 0', PRL 1', CM between parameters considered. At correlation study, no correlation was found between Femoral and Lumbar T-Score and PRL levels, testosterone, Cab dose, and BMI; while age was indirectly and significantly correlated with serum calcium levels ($r=-0.39$; $P=0.019$) and PRL values were directly and significantly correlated with Cab mean dose ($r=0.55$; $P=0.003$) and with disease duration ($r=0.404$; $P=0.036$). No other significance was found in the regression analysis.

Conclusions

In accordance with previous studies, hyperprolactinemia seems to be an independent risk factor on the alteration of bone mineral density and consequent fracture risk. As expected, a reduced level of calcium was found with increasing age. Finally, a data of particular interest was the detection of an influence of cabergoline on PTH levels.

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RC7.5

Evaluation and follow-up data of patients diagnosed with hypophysitis: A multicentric nationwide study

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Background
Hypophysitis is a rare group of disease characterized with infla mmation of the pituitary gland. Rarity of the disease obviates development of a treatment strategy. We aimed to present the nationwide data of the demographics, clinical and radiological characteristics, treatment modalities and responses of the patients diagnosed with hypophysitis in a retrospective manner.
Methods
The endocrinology clinics all over the country were invited to the study. The patients' charts and computer-based records were retrospectively reviewed by an endocrinologist from each center. Protocol templates were used for data collection which were analyzed by the principal investigators.
Results
The data of 154 patients (109 female, 45 male) with a median (range) age of 37 (16-82) years from 30 clinics was analyzed. The most common symptoms were headache (57.1%), polyuria-polydipsia (47.4%), and fatigue (30.5%). The most common pituitary MRI findings were stalk thickening (67.6%), increased contrast enhancement (34.5%), and absence of neurohypophyseal bright spot (31.1%). The diagnosis of 110 patients was based on clinical and radiological evaluation, while 8 were performed biopsy, and 36 surgery. 115 patients (90 female, 25 male) had primary hypophysitis, 31 secondary hypophysitis (13 histiocytosis, 8 sarcoidosis, other:10), and 8 were undetermined. The median (range) follow-up was 23.5 (1-300) months. 52 (45.2%) patients presumably had lymphocytic hypophysitis, 21 of whom had histologic verification. 71 patients (62.8%) with primary hypophysitis had at least one anterior pituitary hormone deficiency, and 46 (40.7%) had diabetes insipidus. In primary hypophysitis group 54 patients were followed without interventions, and 50% (23/46) had radiologic improvement. 26 patients were started on steroid therapy with a median (range) metilprednisolone starting dose of 100 mg (40-1000), and a median treatment duration of 6 weeks (2-12). 64.7% (11/17) of the patients had radiologic improvement. The patients treated with glucocorticoids had more severe MRI findings at presentation compared to those that were followed without interventions. 36 patients with primary hypophysitis were performed surgery. The main indication was presence of compression symptoms and/or indeterminate diagnosis in 24 (66.6%) patients, while unresponsiveness to steroid therapy and assumption of a functional adenoma were other reasons. 2 patients had radiologic progression despite surgery followed by steroid therapy.
Conclusion
The study provides follow-up data of a nationwide large cohort diagnosed with hypophysitis. Clinically and radiologically mild cases might be followed without interventions. Glucocorticoids proved efficacious in some cases though the optimal dose and duration are not known. Surgery may be preferred for treatment-resistant and indeterminate cases.

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RC7.6

Acquired Hypothalamic dysfunction in childhood: "What do patients need? "

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Introduction
Hypothalamic dysfunction (HD) during childhood can occur due to (treatment of) a suprasellar brain tumor. HD may not only result in pituitary dysfunction, but also in severe hyperphagia, decreased energy expenditure, diabetes insipidus with adipsia, disturbance of circadian rhythm, temperature dysregulation and behavioral problems. Currently there is no effective treatment for HD while HD has major impact on quality of life. To provide optimal care and to design the most relevant studies, aiming to improve quality of life, it is essential to understand the patients' needs . For this reason, an online questionnaire was conducted, to address the most relevant problems and the unmet needs of patients with HD as well as their perspective on future research and clinical approaches.
Methods
Through the different patient advocacy groups, SIOPe craniopharyngioma working group and the ENDO-ERN platform, a world-wide online survey was disseminated to patients with childhood onset HD following treatment for a brain tumor (April 2022 – October 2022).
Results
In total, 361 patients responded to the survey. Most were above 18 years old when filling out the questionnaire (63.7%), and 71.7% were diagnosed more than six years ago. The majority had been diagnosed with a craniopharyngioma (78%). In total 63% had panhypopituitarism. Obesity and fatigue were considered the most important health problems for patients (in respectively 48.8% and 46.5%). Patients indicated to want more support with food choices and diet, exercise and psychosocial assistance. In total 18% of patients indicated that there is a lack of information by their doctors on the disease and 14% reported a need for more psychological support. According to the patients, there is a need for more centralized care. Patient ideas for future research included (1) alternative ways for hormone administration (without injection, hydrocortisone by pump), (2) new treatments for hypothalamic obesity, (3) ways to improve early diagnosis of the suprasellar tumor.
Conclusion
According to the patient perspective, the care of patients with acquired HD should be more centralized and from an early stage onwards there should be more focus on quality of life and late consequences. Research should focus on fatigue, hypothalamic obesity and early diagnostics. Ideally, care should be delivered by doctors who have a holistic view of the patient in a multidisciplinary expert team where information is shared with patients but also between subspecialists.

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Rapid Communications 8: Calcium and Bone

RC8.1

Targeting adipocyte ESRRA rebalances bone and marrow adipocyte homeostasis through opposite regulation of LEPTIN and SPP1

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Osteoporosis is a progressive disease characterized by excessive bone loss which is often accompanied by augments in marrow adiposity as a result of estrogen deficiency, metabolic abnormalities or medications. Nuclear receptor estrogen-related receptor alpha (ESRRA) has a demonstrated role in energy homeostasis and fat metabolism. To determine if ESRRA is a potential therapeutic target for regulating fat-bone balance, we generated an adipocyte-specific ESRRA knockout mice (ESRRAAKO) by using an Adiponectin recombinase which labels mature adipocytes within peripheral adipose depots and most bone marrow adipocytes (BMAds) derived from mesenchymal stem cells (BMSCs). We found that ESRRAAKO mice were protected from bone loss after ovariectomy or diet-induced obesity (DIO). Interestingly, marrow adipocytes were more resistant to estrogen deprivation and overfeeding than visceral white adipose tissue (WAT) in ESRRAAKO mice. Furthermore, $CD31^{hi}$ $Emcn^{hi}$ vessel (termed as type H vessels) formation was improved in ESRRAAKO mice following ovariectomy or DIO. By using microCT analysis, bone histology, immunofluorescence staining, calcein double labeling and ELISA assays, we demonstrated that loss of ESRRA in adipocytes alleviated fat-bone imbalance with reduction of marrow adipocytes expansion, stimulation of type H vessel formation and enhancement of trabecular bone formation. By using methods such as RNA-seq, Duo-luciferase reporter, chromatin immunoprecipitation assay, qRT-PCR and immunofluorescence staining of adipose sections, we revealed that ESRRA oppositely regulates transcriptional expression of *Spp1* and *Leptin* within both WAT adipocytes and BMAds. SPP1 has been characterized as an negatively charged matrix glycoprotein preferring to anchor in bone environment. We performed transwell assay and matrigel tube formation assay of endothelial cells (ECs) cultured in conditioned medium from either gWAT or BMAds supplemented with anti-SPP1 neutralizing antibody or recombinant SPP1, and confirmed that increased secretion of SPP1 from ESRRAAKO mice enhancing the ability of ECs to migrate and form capillary-like network structures compared to control mice. On the other hand, LEPTIN is known to promote bone adipogenesis by LEPTIN/lepR signaling in BMSCs. In contrast, we further revealed that ESRRA ablation resulted in the suppression of LEPTIN secretion from adipocytes conferring osteogenic differentiation while constraining adipogenic differentiation of BMSCs. Finally, pharmacological treatment in DIO mice with an ESRRA specific inverse agonist compound 29 enhanced bone formation coupled with a reduction of MAT expansion. Collectively, our results proved that adipocyte

ESRRA inhibition favored bone formation and may have important therapeutic implication in bone diseases associated with fat-bone imbalance.

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RC8.2

Sarcopenia, low bone mineral density and hidden obesity in young adult Men Living with HIV (MLWH): prevalence and relationship with sex steroids

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Background

HIV is associated with decreased bone mineral density (BMD) and decreased muscle mass. Osteoporosis and sarcopenia often co-exist and their onset is multifactorial. Sex steroids play a key role in the homeostasis of bone health and body composition in HIV-uninfected men, but data in MLWH are scanty.

Aim

To investigate the frequency of low BMD and sarcopenia and their relationship with gonadal function in MLWH younger than 50.

Methodology

Prospective, cross-sectional, observational study on MLWH with ongoing antiretroviral therapy. Body composition and BMD were obtained by dual-energy X-ray absorptiometry (DXA). Sarcopenia was defined as appendicular lean mass/height^2 (ALMI) <7.26 kg/m^2; low BMD was defined for Z-score <2.0 at lumbar or femoral site. Patients were classified according to body mass index (BMI) and body fat percentage: hidden obesity was defined wherein BMI was 18.5-25.0 kg/m^2 and the body fat percentage was $>20\%$. Serum total testosterone (TT) and estradiol (E2) were measured by liquid chromatography-tandem mass spectrometry; free testosterone (cFT) was calculated by Vermeulen equation.

Results

A total of 316 MLWH aged 45.3 ± 5.3 years were enrolled. BMD was normal in 265 MLWH (86.0%) and reduced in 43 (14.0%); sarcopenia was detected in 107 MLWH (33.8%). Sarcopenic MLWH had lower cFT ($P=0.002$), E2 ($P=0.002$), E2/T ratio ($P=0.017$), and reduced BMD at both lumbar and femoral site compared to non-sarcopenic patients. Furthermore, sarcopenic patients had lower BMI ($P<0.001$) along with increased total fat percentage ($P=0.038$); accordingly, the prevalence of hidden obesity was greater in sarcopenic than non-sarcopenic subgroup (71.0% vs 37.7%; $P<0.001$). The E2/TT ratio was lower in patients with low BMD compared to those with normal BMD ($P=0.023$), although TT, E2, and cFT did not differ. Patients with lower E2/TT values had an increased likelihood risk of sarcopenia ($P=0.044$) and low BMD ($P=0.025$). No difference was found for age and HIV duration comparing patients for low BMD or sarcopenia. Finally, ALMI was directly associated with BMD Z-scores at any site.

Conclusions

Sarcopenia and low BMD are common findings among young adult MLWH and these conditions are strictly related each other. Within the multidimensional network of factors leading to reduced BMD and lean mass, an imbalanced E2/TT ratio seems to be more relevant rather than TT or E2 alone. The prevalence of hidden obesity is high, especially in sarcopenic MLWH, and it may be overlooked by weight measurement alone with a consequent undermanagement of the increased cardiometabolic risk.

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RC8.3

CYP24A1 mutation as a rare cause of hypercalcemia during pregnancy

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Clinical case

A 27-year-old pregnant woman (24 weeks of gestation) was investigated as her Hb level (87 g/l) was low. Laboratory work-up revealed severe, non-PTH dependent hypercalcemia (see Table). This was her first pregnancy, and serum calcium measured once previously 12 years earlier had been normal. The patient had symptoms of increased thirst, constipation and hyperemesis.

Lab	Result	Reference range
S-Ca-ion	1.76 mmol/l/pH7.4	1.16-1.3
eGFR	66 ml/min/1.73 m^2	>89
24-h U-Ca	11.72 mmol	1.3-6.5
fP-PTH	<4.6 ng/l	18-80
P-PTHrP	<0.50 pmol/l	<1.3
S-D-25	84 nmol/l	>50
S-D-1,25	238 pmol/l	48 – 190
S-LZM	15 mg/l	<12

Diagnostic work up and Treatment

Rehydration and close monitoring of calcium concentration was initiated. Hematological investigations, including bone marrow biopsy, were normal. Whole body MRI did not reveal any malignancy. In addition to PTH, PTHrp concentration was also suppressed. The patient was put on oral **prednisolone**, but the effect was not sustained. Next, genetic causes of hypercalcemia during pregnancy were considered. Both FHH and MEN-1 syndrome are characterized by PTH-dependent hypercalcemia. A CYP24A1 mutation was suspected, and **low-calcium diet** was initiated on the 30th gestational week, before the results of genetic analysis were obtained. Mutation screening of the *CYP24A1* gene revealed a homozygous inactivating mutation c.1186C>T; p.(Arg396Trp). The patient was started on a **diet strictly avoiding both calcium and vitamin D**, which lowered her serum calcium to a nadir of 1.28 mmol/l/pH7.4. The fetus was regularly monitored during pregnancy and no signs of growth retardation were noted. The patient delivered a healthy child at 38 weeks of gestation. After delivery, the patient's calcium levels remained normal on a regular diet. The patient's sister was found to be heterozygous for the same gene mutation. Her calcium levels remained normal during pregnancy.

Discussion

During pregnancy, intestinal calcium absorption in the mother almost doubles to ensure the requirements of the fetus, which is mediated by increased S-D-1,25 and estrogen concentrations. Inactivating mutation in *CYP24A1*, encoding vitamin D-24-hydroxylase, can further accumulate active vitamin-D metabolites and present as hypercalcemia during pregnancy. In addition, the amount of vitamin D and calcium supplements used may influence calcium concentrations during pregnancy.

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RC8.4

Encaleret (CLTX-305) normalized mineral homeostasis parameters in patients with autosomal dominant hypocalcemia type 1: Results over 12 months in a phase 2 study (NCT04581629)

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Autosomal dominant hypocalcemia type 1 (ADH1), caused by gain-of-function calcium-sensing receptor gene (*CASR*) variants, is characterized by low parathyroid hormone (PTH) levels, hypocalcemia, hypercalciuria, hyperphosphatemia and hypomagnesemia. Conventional therapy (calcium and active vitamin D) worsens hypercalciuria, which may result in renal complications. Calcilytics, such as encaleret, are negative allosteric modulators of the calcium-sensing receptor (CaSR). They decrease the hypersensitivity of ADH1 variants to extracellular calcium and normalize biochemical abnormalities in rodent models of ADH1. This Phase 2b open-label study examined the effect of the oral investigational calcilytic encaleret on mineral homeostasis in participants with ADH1. It was comprised of 3 periods followed by a long-term extension (LTE). Conventional therapy was discontinued prior to encaleret initiation. Periods 1&2 examined dose-finding and safety/tolerability. Dosing was optimized and safety and efficacy were assessed over 24 outpatient weeks in Period 3 (P3); all participants continued in the LTE. Thirteen adults with ADH1 were enrolled. Encaleret was individually titrated to normalize albumin-corrected calcium (cCa) and minimize hypercalciuria. Encaleret was well-tolerated with no serious adverse events reported. There were no treatment discontinuations or withdrawals prior to the LTE; one participant withdrew during the LTE for family planning. The mean $\pm$ SD encaleret sulfate dose at week 24 of P3 (P3W24, $n=13$) was 86 ± 70 mg BID and remained stable through month 6 of the LTE (LTEM6, $n=12$; 75 ± 66 mg BID). Twenty-four hour mean $\pm$ SD values from P3W24 and LTEM6 compared to baseline are shown. This study represents a molecularly-

(Abstract RC8.4)

Parameter	Baseline	P3W24	LTEM6
Parathyroid hormone (nl 10-65 pg/ml)	6.1±8.0	23.2±23.0*	42.3±13.6**
Albumin-corrected calcium (nl 8.4-10.2 mg/dl)	7.1±0.4	8.9±0.5**	9.2±0.5**
24-hr Urine calcium (nl<250-300 mg/d)	426±254	202±83**	180±101**
Phosphorus (nl 2.3-4.7 mg/dl)	4.5±1.1	3.7±0.5**	3.2±0.6**
Magnesium (nl 1.6-2.6 mg/dl)	1.7±0.2	2.0±0.2**	2.0±0.2**
Collagen cross-linked C-telopeptide† (pg/ml)	266±161	744±565**	1074±756**
Procollagen type 1 N-propeptide‡ (mg/l)	27±12	104±87**	93±57**
24-hr Urine citrate†† (nl<450-550 mg/d)	487±254	439±224	313±141*

*=$P<0.05$;**=$P<0.01$; †CTX: men 93 – 630 (31 – 50 years), 35 – 836 (51 – 70 years); women: 25 – 573 (pre-menopausal), 104 – 1008 (post-menopausal) ; ‡P1NP: men: 22 – 87: women: 19 – 83 (pre-menopausal), 16 – 96 (post-menopausal); ††Urine citrate: Period 2, Day 1 collection was baseline

targeted, precision medicine approach to the treatment of ADH1. The consistent and sustained results over 12 outpatient months establish a clinically meaningful efficacy, tolerability, and safety profile for encaleret as a potential treatment for adults with ADH1.

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RC8.5

Treatment of chronic hypoparathyroidism by Eneboparatide, a novel PTH receptor-1 agonist: Results from a phase 2a study

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Background
Conventional therapy for chronic hypoparathyroidism (cHP) is often unable to maintain stable normal serum calcium (Ca) levels for a full 24 h, to control symptoms, to prevent the detrimental long-term effects on the kidney and to preserve normal bone architecture. Eneboparatide (AZP-3601) is a novel 36-amino-acid peptide specifically designed to activate the R^0 conformation of the PTH receptor 1, that results in a prolonged calcemic response and a sustained reabsorption of urinary calcium (uCa). We report the results of two consecutive cohorts (C1 and C2) of cHP patients enrolled in a phase 2 multi-center open-label study.
Methods
Patients conventional therapy was adjusted to have albumin-adjusted serum Ca (sCa) within the target range of 7.8 to 9.0 mg/dl before treatment with eneboparatide. From Day 1 onwards, patients received a daily sc. administration at a starting dose of 20 µg (C1; $n=12$) or 10µg eneboparatide/-day (C2; $n=16$), while reducing oral Ca and active vitamin D (vitD) intake. Up-titration to a maximum of 60 µg (C1) or 80 µg/day (C2) was allowed. 24 hr-uCa, serum bone biomarkers (s-CTX and P1NP) were assessed. DXA scan was performed in C2.
Results
24 patients (18 women), with a mean (SD) age of 56 (11) years and mostly post-surgery etiology were taking on average 0.61 (0.26) µg/day active vitD and 1733 (1442) mg oral Ca at baseline. Eneboparatide was well tolerated with no serious adverse events. In C2 the 10µg starting dose required an earlier up-titration to 20µg in most patients. After 3-month treatment with eneboparatide, 88% of patients were off active vitD and oral Ca supplements ($\leq$500 mg/day) while mean sCa was maintained within the target range. Mean reduction in 24 hr-uCa from baseline after 3 months was 63% and 58%, in C1 and C2, respectively, including normalization in all 6 patients with hypercalciuria at baseline in C1 and 6 of 7 patients in C2. Bone biomarkers increased and remained within the normal range for the duration of the study, averaging 352 (166) and 477(252) ng/l for CTX (ULN=900 ng/l)) and 54(17) and 65(31) ng/l for P1NP (ULN=74 ng/l), in C1 and C2 at D84 respectively. In C2, BMD, T and Z scores did not significantly change at 3 months.
Conclusion
Eneboparatide allowed independence from conventional therapy and maintenance of sCa within a target range primarily via enhanced reabsorption of uCa while producing a balanced resumption of bone turnover. Data support advancement to Phase 3 and selection of 20µg as starting dose.

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RC8.6

Eneboparatide, a novel PTH 1 receptor agonist, induces rapid reduction and normalization of urinary calcium in chronic hypoparathyroid patients

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Background
Conventional therapy with oral calcium (Ca) and active vitamin D (vitD) supplementation for chronic hypoparathyroidism (cHP) can induce or aggravate hypercalciuria and may lead to detrimental long-term renal complications. Eneboparatide (AZP-3601) is a novel 36-amino-acid peptide with a short half-life designed to activate the R^0 conformation of the PTH 1 receptor which produces a prolonged calcemic response. This phase 2a study examined the effects of eneboparatide on urinary Ca (uCa) excretion in two consecutive cohorts (C1 and C2) of cHP patients.
Methods
Following an optimization period, during which Ca and active vitD doses were adjusted to achieve baseline albumin-adjusted serum calcium within the target range of 7.8 to 9.0 mg/dl, patients received a daily sc. injection of eneboparatide at initial doses of 20 µg/day (C1) or 10 µg/day (C2), while simultaneously reducing their Ca and active vitD intake. Subsequent up-titration to a maximum daily dose of 60 µg (C1) or 80 µg (C2) was allowed. Twenty-four-hour urinary Ca excretion (24 h-uCa), fractional excretion of Ca (FECa), 24 h-urinary phosphate (24 h-uP) and serum phosphate (sP) were assessed at baseline and at D84. Pooled data from 24 patients who completed the study are presented here.
Results
Twenty-four patients (18 women) aged (SD) 56 (11) years were taking 0.61 (0.26) µg/day active vitD and 1733(1442) mg oral Ca at baseline. At D84, active vitD and oral Ca were discontinued in 88% of patients, while mean albumin-adjusted serum calcium remained within the target range. Mean 24 h-uCa decreased from 325 (172) mg/24 h at baseline to 207 (107) mg/24 h and 130 (91) mg/24 h at D14 and D84, respectively. In 13 patients with hypercalciuria at baseline, we observed

a 67% reduction of 24 h-uCa at D84 and a normalization of 24 h-uCa in 12 (92%). From baseline to D84, mean FECa decreased in the entire population and in patients with hypercalciuria. Between baseline and D84, 24 h-uP excretion increased from 721 (331) mg/24 h to 794 (238) mg/24 h while mean sP decreased from 4.3 (0.8) mg/dl to 3.7 (0.6) mg/dl.
Conclusion
These data demonstrate that eneboparatide treatment maintained sCa within the target range after withdrawal of conventional therapy, likely acting via a potent effect on the tubular reabsorption of calcium. The observed significant improvement in both uCa and sP is expected to translate to a clinically meaningful benefit for cHP patients in the long-term.

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Rapid Communications 9: Adrenal and Cardiovascular Endocrinology 2

RC9.1

Symptoms of glucocorticoid-induced adrenal insufficiency – A systematic evaluation of clinician- and patient-reported symptoms and their rated relevance

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Context
Glucocorticoid-induced adrenal insufficiency is the most frequent type of adrenal insufficiency, but its symptomatology has not been thoroughly studied.
Objective
To describe the predominant symptoms experienced by patients with glucocorticoid-induced adrenal insufficiency and rate these symptoms' significance for patients' perceived need for supplemental hydrocortisone stress dose.
Methods
The 80 symptoms in the Patient-Reported Outcomes version of the common Terminology Criteria for Adverse Events (PRO-CTCAE) questionnaire, were presented to 11 endocrinologists from four Danish tertiary endocrine referral centres. The endocrinologists rated the symptoms' relevance and could add additional symptoms. Symptoms with a mean score ≥ 1 ("minor relevance") were evaluated by a Delphi panel including 3 senior investigators who excluded symptoms found irrelevant for a need for hydrocortisone stress doses. The remaining items were presented to adult patients with longstanding glucocorticoid-induced adrenal insufficiency receiving hydrocortisone replacement treatment. During interviews, participants first described their symptoms of glucocorticoid-induced adrenal insufficiency and subsequently rated the PRO-CTCAE symptoms from 1 (completely irrelevant) to 5 (very important) according to the *significance* in realising the need of hydrocortisone stress doses. New symptoms were added for the next participants to rate. Importance scores were calculated as the percentage of the participants experiencing the symptom times the mean significance rating.
Results
The PRO-CTCAE symptom review by 11 endocrinologists identified 17 relevant symptoms of glucocorticoid-induced adrenal insufficiency. The Delphi round removed three symptoms. Thirty patients (20 women) were included with mean (SD) age 58.4 (14.2) years and with median (range) duration of glucocorticoid-induced adrenal insufficiency of 5 (0.5-31) years, after glucocorticoid treatment of mainly asthma and rheumatological disorders. They reviewed the 14 symptoms and added 14 symptoms. The symptoms most frequently experienced were fatigue (87%), feeling generally unwell (80%), weariness (80%), difficulty concentrating (63%), and nausea (60%). The symptoms with the highest mean significance scores were dizziness (4.33), nausea (4.29), vomiting (4.20), fatigue (4.15), and feeling generally unwell (4.09). The symptoms with the highest importance scores were fatigue (360), feeling generally unwell(325), weariness (293), nausea (253), and difficulty concentrating (250).
Conclusions
The presented new knowledge of the patients' self-perceived symptoms of glucocorticoid-induced adrenal insufficiency can improve the clinical understanding of the condition. Additionally, this systematically investigation of symptoms has led to the development of a symptom measurement tool used in two ongoing clinical trials on glucocorticoid-induced adrenal insufficiency.
Funding
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RC9.2

Frequency of stress dose adjustment and adrenal crisis in children and adults with congenital adrenal hyperplasia

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Background
Patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CAH) require lifelong glucocorticoid replacement therapy, including stress dose adjustment to prevent life-threatening adrenal crises (AC). Previous studies indicate a high incidence of inadequate stress dose adjustment and AC in patients with CAH. The aim of this study was to prospectively assess AC incidence, frequency and details of stress dose adjustment as well as knowledge of the disease in adult and paediatric patients with CAH as well as their caregivers.
Methods
A total of 38 children and their caregivers and 162 adults with CAH were included in this prospective, multi-centre study. To collect data on frequency, cause, duration and dosage of dose adjustments and the occurrence of AC, a patient diary was used. In case of AC, additional medical records were reviewed and patient interviews were conducted. Additionally, it was assessed if current sick day rules of the German Society of Endocrinology (DGE) were followed adequately. Knowledge of the disease was assessed using the CAH Knowledge Assessment Questionnaire (CAHKAQ) in the German version.
Results
We found an AC incidence of 8.4 per 100 patient years (py) in 145 adults and 5.1 in 100 py in 29 children. In the adult cohort, a total of 195.4 dose adjustments per 100 py were recorded, in the children cohort a total of 169.7 per 100 py. According to the DGE recommendations, in 24.1% of cases in adult patients dose adjustment was unnecessary and in 33.9% of cases dosage of adjustment was incorrect. A total of 34.8% of dose adjustments in adults were performed correctly. There was a significant positive correlation of the frequency of dose adjustments and the incidence of AC ($r = .24$, $p = .011$) and CAHKAQ Score ($r = .23$, $p = .014$) in adults. In the children cohort, 4.3% of dose adjustments were unnecessary and in 19.1% of cases dosage of adjustment was incorrect. A total of 72.3% cases of dose adjustments in children were conducted correctly.
Conclusion
Children and adults with CAH show a high incidence of AC and stress dose adjustments. The majority of stress dose adjustments in adults were not in accordance to the recommendations of the DGE, whilst in children the majority of dose adjustments was conducted correctly. These findings underline the need for structured and repeated education of patients to avoid inadequate dose adjustments while preventing AC, with particular focus on the timing of transition.

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RC9.3

Fingerprints of increased susceptibility to adrenal crises in patients with chronic adrenal insufficiency

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Background
Potentially fatal adrenal crises (AC) still occur in educated patients with adrenal insufficiency (AI). Identifying predisposing factors is necessary for prevention in this patient population.

Objectives
Investigating clinical and biochemical fingerprints of increased susceptibility to AC.
Material and methods
Our study population included 260 patients with chronic AI, classified as high and low risk according to the frequency of experienced AC per patient-years. Besides classical clinical and biochemical data, following parameters were assessed: 24 h urinary cortisol, salivary cortisol day profile, steroid profile in serum, plasma and urinary catecholamines, polymorphisms (SNPs) of the glucocorticoid receptor (NR3C1), mineralocorticoid receptor (NR3C2), HSD11B1, HSD11B2 and FKBP5, information on therapy adjustments and patient education.
Results
27% ($n=71$) of the patients were classified as having a high risk for AC. This group was treated with higher glucocorticoid replacement doses (12 ±4 vs 11 ±4 mg hydrocortisone-equivalent /m^2/day, $P=0.03$) and displayed significantly higher salivary cortisol levels in the morning (pre-dose) and at noon compared to the low risk group (morning 0.034 (0.034-0.23) vs 0.038 (0.034-1.6) µg/dl, $P=0.02$, noon: 0.36 (0.03-5.5) vs 0.7 (0.03-3.4), $P=0.04$). Plasma metanephrine levels were significantly lower in the high risk group (17 ±12 vs 22 ±12 ng/, $P<0.01$). Overall, prevalence of risk genotypes of the analysed SNPs was low. Several NR3C1, NR3C2 und HSD11B1 SNPs related to impaired steroid sensitivity were significantly associated with AC frequency. Analysis of dose adjustments performed by patients themselves in case of AC revealed a significantly higher frequency of self-injected hydrocortisone in high risk patients (56% vs 19%, $P=0.021$), whereas low risk patients increased their oral doSemore often (81% vs 52%, $P=0.06$). Frequency of prophylactic stress dose adjustments (eg for intense physical activity) over a period of 6 months was also significantly higher in high risk compared to low risk patients (100% vs 73%, $P<0.01$).
Conclusion
The higher glucocorticoid replacement dose and higher frequency of prophylactic dose adjustments seen in high risk patients fit to previous observations and might simply reflect increased caution but could also be regarded as an indicator of increased vulnerability, as also suggested by lower plasma metanephrine levels. The association between the risk for AC and SNPs of both glucocorticoid and mineralocorticoid receptor as well as HSD11B1 also implies a genetic susceptibility to AC. These observations require validation in prospective studies.
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RC9.4

Dysregulations in CLOCK genes in immune cells in congenital adrenal hyperplasia depending on the type of glucocorticoid replacement regimens

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Background
Glucocorticoid (GC) substitution therapy in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CAH) is not able to perfectly mimic physiological circadian profiles. Unphysiologically high doses, as well as unphysiological variations in GC concentrations might cause adverSemetabolic, cardiovascular and immunological effects. Previous publications have demonstrated dysregulations in immune cell profiles of patients with primary adrenal insufficiency (PAI) under standard hydrocortisone (HC) therapy most likely via dysregulations of clock gene expression. GCs have been shown to modulate expression of certain clock genes and are involved in creating a stable 24-hour rhythm of various cell types and physiological pathways. Thus, changes in GC profiles might differentially affect cell functions.
Methods
Cross-sectional single-center study including 75 patients with CAH and 50 sex- and BMI- matched healthy controls. Patients were divided into three groups depending on type of glucocorticoid medication: HC ($n=28$), prednisone/prednisolone ($n=33$) and modified-release hydrocortisone treatment (MR-HC $n=14$). Peripheral blood mononuclear cells (PBMCs) were isolated from all subjects using a Ficoll density gradient centrifugation within 4 hours after sample collection. Real-time qPCR was carried out for expression of the following nine clock genes (*CLOCK*, *ARNTL*, *CRY1*, *CRY2*, *NR1D1*, *WEE1*, *TIMELESS*, *CREB1*, *PER3*).
Results
CLOCK gene mRNA expression was reduced in *CLOCK* ($P<0.0001$), *CRY1* ($P<0.0001$), and *TIMELESS* ($P<0.0001$) in patients versus controls regardless of type of GC medication used. *WEE1* and *CRY2* mRNA expression were only reduced in patients using conventional GCs as HC (*WEE1* $P=0.0018$, *CRY2* $P=0.0002$) and prednisone/prednisolone (*WEE1* $P<0.0001$, *CRY2* $P=0.0001$). Compared to controls, *ARNTL* mRNA expression was only reduced in patients treated with prednisone/prednisolone ($P=0.0436$). There was no change in *NR1D1*, *CREB1* or *PER3* expression between the different treatment groups and controls. Least changes in mRNA expression compared to healthy controls were observed in patients treated with MR-HC (*CLOCK* $P=0.0001$, *TIMELESS* $P=0.0003$, *WEE1* $P=0.7960$, *CRY2* $P=0.1119$).
Conclusion
CAH patients receiving conventional therapy exhibit dysregulations of CLOCK gene expression in PBMCs. Least disturbance of CLOCK gene mRNA expression compared to healthy controls was observed in those patients treated with MR-HC preparations. Further studies are needed to explicitly analyze these effects in CLOCK gene expression on the clinical phenotype including adverSemetabolic, cardiovascular and immunological events.
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RC9.5

Higher maternal cortisol associated with lower blood pressure in offspring from 3 months to 5 years of age in the odense child cohort

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Background
Synthetic glucocorticoid exposure in late pregnancy may be associated with higher blood pressure in offspring. We hypothesized that endogenous cortisol in pregnancy relates to offspring blood pressure (OBP).
Objective
To investigate associations between maternal cortisol status in 3rd trimester pregnancy and OBP.
Methods
We included 1,317 mother-child pairs from Odense Child Cohort (OCC), an observational prospective cohort. Serum (s-) cortisol and 24 h urine (u-) cortisol and cortisone were assessed in gestational week 28. Offspring systolic (SBP) and diastolic (DBP) blood pressure were measured at age 3, 18 months and 3 and 5 years. Associations between maternal cortisol and OBP were examined by mixed effects linear models.
Results
All significant associations between maternal cortisol and OBP were negative. In boys in pooled analyses (3 and 18 months, 3 and 5 years of age), 1 nmol/l increase in maternal s-cortisol was associated with average decrease in SBP of -0.003 mmHg (95% CI: -0.005; -0.0003)) and DBP of -0.002 mmHg (95% CI: -0.004; -0.0004)) after adjusting for confounders. At 3 months of age, higher maternal s-cortisol was significantly associated with lower SBP (β=-0.01 mmHg (95% CI: -0.01; -0.004)) and DBP (β=-0.010 mmHg (95% CI: -0.012; -0.011)) in boys after adjusting for confounders and remained significant after adjusting for potential intermediate factors.
Conclusion
We found temporal sex dimorphic negative associations between maternal s-cortisol levels and OBP, with significant findings in boys. We conclude that physiological maternal cortisol is not a risk factor for higher blood pressure in offspring up to 5 years of age.
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RC9.6

Immunohistochemical analysis of somatostatin receptor 2 and the tumor microenvironment in a large set of pheochromocytomas and paragangliomas

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Introduction
Pheochromocytoma and paraganglioma (PPGL) are rare endocrine tumors with few effective treatment options for malignant cases. Novel therapeutic indications, such as 177Lu-DOTA-TATE and immune checkpoint inhibitors (ICIs) for patients with PPGL, have been investigated in several clinical trials. Emerging evidence shows that somatostatin receptor 2 (SSTR2) in other cancer types correlates with the tumor microenvironment (TME) activation and could be a predictive biomarker of ICIs as well as 177Lu-DOTA-TATE. Among gastroenteropancreatic neuroendocrine tumors, SSTR2 expression is associated with a low-grade tumor. However, the association between the expression of SSTR2 and TME and clinical features in PPGL has not yet been reported.
Methods
We studied the immunohistochemical expression of SSTR2A and the immune cells, including tumor infiltrating lymphocytes (CD4 and CD8), tumor associated macrophages (CD68 and CD163), and angiogenic markers (CD31 and intratumoral hemorrhage areas) using specific antibodies on archived formalin-fixed, paraffin-embedded tissue of tumor samples in 53 patients with PPGL diagnosed between 1988 and 2020 in two national center hospitals in Japan. We compared those data with clinical and histopathological factors.
Results
The cohort consisted of 23 (43.4%) patients with pheochromocytoma and 30 (56.6%) patients with paraganglioma, including 27 aggressive tumors (metastasis or local invasion) and 29 functional PPGLs with a mean follow-up duration of 81.1 ± 82.6 months. The median age was 46 (range, 17-80), and 62.3% of the patients were female. The expression of SSTR2A was strongly increased in 19 samples (35.8%). The positive staining score for SSTR2A was significantly more frequently associated with aggressive tumors (78.9% vs 35.3%, $P=0.004$), high Ki-67 index (5.15 [1.6 – 29.6] vs 2.35 [0.2 – 46.9], $P=0.001$), high GAPP score (6.40 ± 1.80 vs 4.84 ± 1.97, $P=0.013$), and high PASS score (9.33 ± 3.52 vs 6.94 ± 3.35, $P=0.029$) compared to the negative staining score for SSTR2A. No correlation was found between the staining score for SSTR2A expression and other factors: functional status, primary tumor sites, tumor size, intratumoral hemorrhage areas, and the positive cells of CD4, CD8, CD31, CD68, and CD163.
Conclusion
SSTR2A could be a predictive marker of more aggressive PPGL and would play an essential role in further clinical investigations in patients with PPGL. Whereas, since SSTR2A was expressed independently of clinical features and TME status, immunohistochemical analysis of SSTR2A for each tumor should be performed for treatment selection.

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Rapid Communications 10: Diabetes, Obesity, Metabolism and Nutrition 2

RC10.1

Gold and cerium oxide nanoparticles reduce liver steatosis and inflammation in rats with steatohepatitis

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Introduction
Metabolic dysfunction-associated fatty liver disease (MAFLD) is characterized by the presence of hepatic steatosis, which can progress to non-alcoholic steatohepatitis (NASH), fibrosis, and hepatocellular carcinoma. There are no licensed therapies to halt MAFLD progression, despite it is becoming the most important etiology for advanced liver disease.
Aim
The aim of the study was to evaluate the therapeutic potential of inorganic nanoparticles (NPs) (cerium oxide [CeO_2NPs], gold [AuNPs] and their combination in the same nanostructure [AuCeO2NPs]) in an experimental model of fatty liver disease.
Methods
Steatohepatitis was induced in Wistar rats by a methionine-choline-deficient (MCD) diet. A first pilot protocol included 10 rats on MCD diet for 3 weeks, which were randomly administered intravenously (iv) with CeO_2NPs (0.25 mg/kg; $n=5$) or vehicle ($n=5$) at weeks 1 and 2. CeO_2NPs significantly reduced hepatic steatosis and IL1β expression, although without changes in transaminases. Therefore, in a second protocol, mesoporous silica ($mSiO_2$) coating of the inorganic NPs was designed to improve their stability and biological effects. The NPs were administered iv (weeks 1 and 2) in 5 groups of 8 animals on MCD diet for 3 weeks (group1: CeO_2NPs@$mSiO_2$, group 2: AuNPs@$mSiO_2$, group 3: $AuCeO_2$NPs@$mSiO_2$, group 4: $AuCeO_2$NPs, and group 5 [vehicle]: $mSiO_2$). Biodistribution of NPs was analyzed by inductively coupled plasma mass spectrometry (ICP-MS). Standard parameters of liver and renal function and lipid profile were measured in a chemistry analyzer (Mindray). The effects on liver steatosis, infla mmation and metabolism were assessed by histological examination, gas chromatography mass spectrometry and the analysis of the expression of 88 genes related to liver steatosis and infla mmation (customized Rat Fatty Liver RT^2 Profiler^{TM} PCR Array, Qiagen).
Results
Biodistribution analysis revealed that cerium and gold accumulated mainly in the liver and spleen. Treatments with AuNPs@$mSiO_2$ and $AuCeO_2$NPs@$mSiO_2$ were the most effective in reducing hepatic steatosis ($49 \pm 2\%$, $50 \pm 1\%$ vs $55.0 \pm 1\%$; $P<0.05$) and ALT levels (114 ± 10, 110 ± 9 vs 190 ± 29 U/l; $P<0.05$). These effects were associated with a significant improvement (fold regulation >1.50; $P<0.05$) on the hepatic expression of 21 (Au@$mSiO_2$) and 50 ($AuCeO_2$NPs@$mSiO_2$) of the 88 analyzed genes, which were mainly related with reduced infla mmatory response and adipokine signalling, and improvements in metabolic pathways involved in oxidative phosphorylation and lipid metabolism and transport.
Conclusion
Treatment with gold and cerium oxide NPs coated with $mSiO_2$ improve hepatic steatosis and infla mmation in an experimental model of steatohepatitis.

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RC10.2

Increased risk of cirrhosis in post-menopausal women with NAFLD

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Background
Non-alcoholic liver disease (NAFLD) affects up to 30% of adults worldwide. With the prevalence of NAFLD increasing after menopause, women aged >55 years are more likely to progress to advanced fibrosis than men. Moreover, liver decompensation secondary to NAFLD is more frequent in women compared to men. However, the causes of these differential outcomes are not fully understood.
Methodology
We performed a retrospective cohort study utilising a database of consecutive patients followed up in the specialist multi-disciplinary NAFLD Clinic at Imperial College Healthcare NHS Trust (London, UK) with their first clinic review between 2009 and 2020. NAFLD was diagnosed either clinically or histologically. Clinical, biochemical, radiological and histological data were collected up to December 2022. Postmenopausal women were defined as women aged ≥55 years at their first clinic visit. Cirrhosis was diagnosed based on a combination of clinical, biochemical and/or radiological features or based on histology, when available. Multivariate logistic regression was performed to identify variables independently associated with cirrhosis. Statistical significance was set at $P<0.05$.
Results
750 patients with NAFLD were included in this study, with a median (IQR) follow-up of 6 (3-8) years; 293 (39%) were female, 323 (43%) Caucasian, 161 (22%) South Asian, 75 (10%) Middle Eastern, median (IQR) age: 52 (42-60) years. At initial clinic review, fewer postmenopausal women (compared to age-matched men) had a Fibrosis-4 (FIB-4) score >1.3 (73% v 84%, $P<0.05$). However, similar proportions of postmenopausal women and age-matched men had an initial liver stiffness measurement ≥8 kPa (64% v 68%, $P=0.27$). Initial prevalence of type 2 diabetes, cardiovascular disease and obesity, as well as use of GLP-1 receptor agonists and SGLT2 inhibitors were similar between the two groups. Overall, postmenopausal women ($n=156$) had increased risks of being diagnosed with cirrhosis (OR 2.18 (95%CI 1.11-4.26), $P<0.05$) when compared to all other patients, as well as compared to age-matched men ($n=149$) alone (OR

2.58 (95%CI 1.14-6.02), $P<0.05$). There were insufficient data on reproductive hormone use for this variable to be included in the analyses.
Conclusions
In this diverse cohort from a tertiary care centre, being a postmenopausal woman is associated with worse outcomes than being a man of any age or a younger woman. These disparities occur despite postmenopausal women presenting to specialised secondary care clinics with similar co-morbidities and receiving similar medication to age-matched men. Therefore, tailored management strategies may be required to improve outcomes in postmenopausal women with NAFLD.

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RC10.3

The maintenance of long-term weight loss after semaglutide withdrawal in obese women with PCOS treated with metformin: A 2-year observational study

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Background
Withdrawal of anti-obesity medication is frequently followed by weight regain due to compensatory biological changes that prevent the maintenance of long-term weight loss. In STEP 1 trial extension participants regained two-thirds of their prior weight loss during the 1-year off-treatment follow-up period after withdrawal of semaglutide 2.4 mg and discontinuation of active lifestyle intervention support. There are some studies implying that metformin might attenuate weight regain after weight loss in women with polycystic ovary syndrome (PCOS). To date, the amount of weight regain after semaglutide withdrawal in obese women with PCOS who continue treatment with metformin has not yet been evaluated.
Aims
We explored changes in body weight, cardiometabolic and endocrine parameters in obese women with PCOS 2 years after semaglutide cessation.
Methods
25 obese women with PCOS (33.7 ± 5.3 years, body mass index (BMI) 36.1 ± 3.9 kg/m^2, mean ± SD) were treated with once-weekly subcutaneous semaglutide 1.0 mg as an adjunct to metformin 2000 mg/day and lifestyle intervention for 16 weeks. At week 16, semaglutide was discontinued. Treatment with metformin 2000 mg/day and promotion of lifestyle intervention were continued during the 2-year follow up period. weight, cardiometabolic and endocrine parameters were assessed to 2 years after semaglutide discontinuation.
Results
During semaglutide treatment phase, weight decreased from 101 (90-106.8) kg to 92 (83.3-100.8) kg. 2 years after semaglutide withdrawal, weight was 95 (77-104) kg. The net weight loss 2 years after discontinuation of semaglutide remained significant when compared to baseline (-7 (-14.3 to -1.5) kg, $P=0.001$). Improvements in cardiometabolic parameters including decrease in total and LDL cholesterol, triglycerides and fasting glucose and glucose after OGTT that had seen during semaglutide-treatment phase, reverted towards baseline two years after semaglutide cessation. The reduction in free testosterone from 6.16 (4.07-9.71) to 4.12 (2.98-6.93) pmol/l ($P=0.004$) and in androstenedione from 6.62 (4.36-8.77) to 5.49 (3.78-6.84) nmol/l, ($P=0.002$), observed during semaglutide treatment phase remained significant for 2 years ($P=0.045$ and $P=0.023$, respectively).
Conclusion
Two years after semaglutide withdrawal, women with PCOS regained one-third of their prior weight loss. Improvements of cardiometabolic variables reverted to baseline, whereas improvement of endocrine parameters achieved during semaglutide treatment phase persisted 2 years after semaglutide cessation. The role of metformin in attenuation of weight regain after semaglutide discontinuation needs to be explored in randomized controlled studies in different insulin resistant populations.

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RC10.4

Kisspeptin does not have detrimental metabolic effects in women

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Background
There is emerging evidence that kisspeptin, a hormone with well-established reproductive effects, may also have important metabolic effects. Acute kisspeptin administration enhances insulin secretion under hyperglycaemic conditions in male rodents and men, and kisspeptin receptor agonism improves steatohepatits in male mice in a rodent model of non-alcoholic fatty liver disease. However, the metabolic effects of kisspeptin may exhibit sexual dimorphism as female (but not male) kisspeptin receptor knockout mice have reduced food intake. Kisspeptin administration has been shown to have no effect on food intake in men, but the effect of kisspeptin on food intake in women has not been investigated.
Methods
We performed a single-blinded randomized controlled crossover study in women with overweight or obesity (BMI >25 kg/m^2) who had not received exogenous estrogens or progestins in the preceding 3 months. Each woman attended two study visits (in random order) following a 14-hour fast. During each study visit either an intravenous infusion of kisspeptin-54 at a rate of 1.0 nmol/kg/hr, or a rate-matched vehicle infusion, were administered for 120 minutes. At regular intervals during the study visits, blood samples were taken. Participants completed visual analogue scales (VAS) to assess hunger prior to the start of the infusions, 30 minutes after the start of the infusions (pre-meal) and 75 minutes after the start of the infusion (post-meal). Forty-five minutes after the start of each infusion, the women were given an *ad libitum* meal. All data are presented as mean ± SD.
Results
Seventeen women (BMI 34 ± 7 kg/m^2, $n=12$ with BMI >30 kg/m^2) completed both study visits. Kisspeptin administration increased LH levels ($P<0.01$), consistent with its known reproductive effects. However, pre-meal estradiol levels were unaffected by kisspeptin administration ($P=0.34$). Kisspeptin administration did not affect appetite pre-meal (hunger VAS scores at 30 mins: kisspeptin 5.2 ± 2.7 vs vehicle 5.9 ± 2.3, $P=0.33$) nor post-meal (hunger VAS scores at 75 mins: kisspeptin 0.5 ± 1.0 vs vehicle 0.4 ± 0.6, $P=0.87$). Food intake was similar during kisspeptin and vehicle infusions (kisspeptin 604 ± 267 kcal vs vehicle 560 ± 217 kcal, $P=0.41$). Glucose ($P=0.97$) and insulin ($P=0.68$) levels were similar during the infusions.
Conclusions
This is the first study to investigate the metabolic effects of kisspeptin in women. Similar to findings in men with BMI <25 kg/m^2, acute administration of a pharmacologically active dose of kisspeptin to women with BMI >25 kg/m^2 did not affect appetite or food intake. These data provide reassurance that kisspeptin receptor agonism is unlikely to have undesirable orexigenic effects in humans.

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RC10.5

Metformin counteracts adverse metabolic effects of glucocorticoids in healthy subjects

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Background
Glucocorticoids are powerful anti-infla mmatory drugs. However, metabolic side effects are common and limit their long-term use. Furthermore, the underlying mechanisms of adverSemetabolic effects are not well known, and this lack of knowledge results in poor treatment. We have previously shown that the antidiabetic drug metformin prevents glucocorticoid-induced metabolic effects in older, sick patients. Here, we investigate metformin in a young and healthy population on high-dose glucocorticoids to establish the role of metformin and identify potential mechanisms counteracting glucocorticoid-induced side effects.
Methods
In a randomized, placebo-controlled, cross-over trial, we compared metformin to placebo during high-dose glucocorticoid treatment in 18 lean, healthy males. All participants received prednisone 30 mg/d for two 8-day periods separated by a 28-day washout period. During one period, participants additionally had metformin; during the other, they received a placebo. Metabolic assessments were performed before and after each study period, including a mixed meal tolerance test (MMTT) and blood metabolomics.

Results
18 male subjects (mean age 27 standard deviation [SD] ±5.2 years, BMI 22.9 ± 1.8 kg/m^2) completed the study. Glucose levels during the MMTT increased with placebo (glucose change in incremental area under the concentration-time curve [AUC] 1.18 ±1.12 mmol/l) but remained stable with metformin (0.02 ±1.25 mmol/l, $P=0.01$). Insulin AUC increased with placebo (94 ±183 pmol/l) but not with metformin (-182 ±168 pmol/l, $P<0.001$). Accordingly, whole-body insulin sensitivity improved with metformin (6.4 ±11.8) compared to placebo (-8.2 ± 10.65, $P<0.001$). Pathway enrichment analysis of metabolites revealed that metformin impacts free fatty acid and bile acid synthesis in the postprandial state.
Conclusion
Metformin prevents the detrimental effects of glucocorticoids on glucose homeostasis by improving insulin sensitivity. Our findings confirm metformin's role in preventing and treating glucocorticoid-induced side effects. Furthermore, the impact of metformin on free fatty acid flux and bile acid synthesis supports that adipose tissue and the gut are sites of metformin action.

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RC10.6

Childhood and adolescent obesity associated with classic congenital adrenal hyperplasia and 21-hydroxylase deficiency

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Introduction
The most prevalent hereditary disease of adrenal steroid production is congenital adrenal hyperplasia (CAH), which is caused by a 21-hydroxylase deficiency. With or without salt wasting, patients with the typical form of CAH exhibit androgen excess. Leptin participates in endocrine and metabolic processes in addition to controlling energy balance. This study examined BMI values for children and teens with CAH in comparison to population-based benchmarks. Current BMI SD scores were associated with potential contributing variables such glucocorticoid therapy, skeletal development, birth weight and length, and parental BMI (SDS). The effects of blood leptin levels that had been adjusted for BMI, gender, and Tanner stage were examined.
Method
80 patients with CAH were a part of this study. All patients underwent replacement therapy and had molecular genetic studies reveal they all had classic CAH. In accordance with current recommendations, the effectiveness of therapy was assessed during follow-up visits based on the clinical presentation and laboratory measurement results. The patients were divided into groups based on their existing metabolic control, simple virilizing, and salt wasting. A commercial radio-immunoassay was used to quantify leptin levels and convert them to SDS. Standard parametric and nonparametric approaches were applied for statistical analyses.
Results
Patients with CAH ranged in chronologic age from 0.20 to 17.9 years. In the entire group, the BMI SDS ranged from 2.6 to 4.2 and was significantly higher than 0.14 subjects had a BMI SDS of 3.0, which showed high prevalence of obesity among patients with CAH than the general population. BMI SDS and chronological age showed a positive correlation. Between children using other medications, the BMI SDS did not substantially differ. Doses of hydrocortisone showed a favorable correlation with BMI SDS. Children receiving medicine did not have high relative probability of having a BMI SDS of 3.0 than those receiving hydrocortisone therapy. Children with obese parents had high relative risk of childhood obesity than children without obese parents (relative risk: 4.85). Serum leptin levels were in the range of 0.11 to 31 g/l, and were strongly linked with Tanner stage, chronologic age, and BMI SDS.
Conclusion
Children and teenagers with CAH are more likely to become obese. Elevated BMI SDS was caused by age, advanced bone age maturation, despite obesity not linked to birth weight and length, serum leptin levels, or glucocorticoid dosage.

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Rapid Communications 11: Late Breaking

RC11.1

Immune checkpoint inhibitors and severe insulinopenic diabetes mellitus: A single center experience

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Introduction
Severe insulinopenic diabetes (SID) is a rare complication of treatment with immune checkpoint inhibitors (ICPI). We describe herein the clinical characteristics, natural history and potential predictors of SID in cancer patients treated with ICPI.
Methods
We identified and retrospectively retrieved pertinent clinical data of all patients who presented with new onset SID following treatment with ICPI between 2015 and 2022 at the Tel Aviv-Sourasky Medical Center.
Results
The study cohort comprised 1621 ICPI-trated patients, of whom 12 patients (0.8%) developed SID. Seven were males (53.8%). Median age was 67 (IQR 60.5-77) years. Eight patients (61.5%) were treated with PD-L1 inhibitors, 3 (23.1%) with PD-1 inhibitors and 2 (15.4%) with a combination of PD1 and CTLA4 inhibitors . Two patients had a prior diagnosis of type 2 diabetes treated with oral medications while 2 other patients had a prior diagnosis of impaired fasting glucose. Three patients (23.1%) developed a concomitant thyroid dysfunction under ICPI. Median time from the initiation of ICPI to presentation of SID was 4 months (IQR 1-9). Five of the patients presented with SID within a month from exposure (38.5%). DKA was the presenting symptom in eleven patients (84.6%), 3 of which were treated with a SGLT2i . One patient (7.7%) died within one week of DKA presentation.
Conclusions
This is one of the largest single center series describing the onset and characteristics of SID following ICPI treatment.

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RC11.2

COVID-19 vaccination and Graves' disease: A population based, matched case-control study

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Objective
Vaccination against coronavirus disease 2019 (COVID-19) an important component of coping with the pandemic. Anecdotal cases and case series reported an association

(Abstract RC11.2)

Age (Years)	Gender	Medication	Prior DM	DKA	Time between exposure and presentation (months)	Underlying malignancy	Concomitant Thyroid dysfunction
82	M	Nivolumab	DM2	+	13	HL	None
74	M	Avelumab	-	-	8	RCC	Hyperthyroidism
58	M	Pembrolizumab	-	+	4	MELANOMA	None
70	F	Pembrolizumab	DM2	+	4	Gastric Adeno CA	None
62	F	Nivolumab	IFG	+	29	Adeno CA Lung	None
66	F	Pembrolizumab	-	+	1	Ovarian Adeno CA	None
82	F	Pembrolizumab	-	+	1	Gastric Adeno CA	None
61	F	Pembrolizumab	-	+	9	Skin SCC	Hypothyroidism
67	M	Durvalumab	-	+	1	NSCLC	Hyperthyroidism
57	F	Ipilimumab + Opdivo	-	+	1	MELANOMA	Unknown
78	M	ipilimumab + Nivolumab	-	+	1	MELANOMA	None
76	M	Nivolumab	IFG	-	9	RCC	None
60	M	Pembrolizumab	-	+	4	Head and Neck SCC	None

This cohort emphasizes the importance of patient education and awareness for this potentially life-threatening complication. Better characterization of ICPI-induced diabetes will improve patient care and enhance our understanding of immune-mediated diabetes.

between COVID-19 vaccination and the development of Graves' disease. We used data from Israel's largest health care organization to determine whether COVID-19 vaccination was associated with the incidence of Graves' disease.
Methods
We analyzed data from Clalit Health Services (CHS), which insures 4.7 million patients. A population-based, matched, case-control study was performed. Cases were defined as adult patients diagnosed with Graves' disease between December 2020 and November 2022. Each case was matched in a ratio of 1:2 with control based on age, gender, and autoimmune disease. Each control was assigned an index date which was identical to that of his/her matched case, which was defined as the date of Graves' disease diagnosis. Time between vaccination date and the diagnosis of Graves' disease/index date was assessed.
Results
A total of 726 patients with Graves' disease were matched with 1452 controls. The median age of the cohort was 40 (interquartile range, 30-53) years, and 25.5% (555/2178) were men. Similar proportions of study patients and controls have received the first, the second and the third dosage of COVID-19 vaccine. Positive test for COVID-19 was detected in 21.2% (154/726) of Graves' disease patients and 19.4% (282/1452) of controls ($P=0.33$). In a univariate analysis, first COVID-19 vaccine was not associated with the incidence of Graves' disease [odds ratio 95% confidence interval: 1.15 (0.92-1.43)]. The mean time between first COVID-19 vaccination and the diagnosis of Graves' disease for cases or index date for controls was not significantly different [275.69 days (standard deviation 144.37) for cases compared to 275.45 days (standard deviation 145.76) for controls].
Conclusions
We have found no association between COVID-19 vaccination and the incidence of Graves' disease. Our study adds data to the thyroid safety of COVID-19 vaccine.

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RC11.3

Mapping endometrial cell-type-specific disease signatures and endometrial organoids in polycystic ovary syndrome

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Women with polycystic ovary syndrome (PCOS) suffer from reduced fertility linked to implantation failure and miscarriage, as well as endometrial cancer, all associated with endometrial dysfunction. We hypothesize that cell-type-specific endometrial dysfunction in insulin-resistant and hyperandrogenic women with PCOS contributes to their endometrial dysfunction and that treatment aimed at improving insulin sensitivity and decreasing androgen excess has the potential to reverse identified alterations. To uncover cell-type-specific disease signatures and molecular pathways for PCOS-specific endometrial dysfunction, we first extracted single-nuclei (sn) from frozen endometrial biopsies taken in the proliferative phase (day 7-10) from controls ($n=5$) and women with PCOS ($n=10$) at baseline and in PCOS after 16 weeks of metformin ($n=7$) or lifestyle management ($n=3$) for snRNA-sequencing. The 10× Genomics protocol allowed us to sequence ≈10,000 nuclei/sample and ≈20,000 reads/nuclei. A total of 248,694 nuclei were captured and 6 major cell types were identified. The three largest cell clusters were i) stromal cells (124,055 nuclei), ii) epithelial cells (105,095 nuclei) and iii) immune cells (13,596), whilst iv) uterine smooth muscle cells, v) endothelial and vi) lymphatic cell clusters consisted of < 3000 nuclei. Subsetting epithelial cells revealed functional lumenal, glandular, and ciliated cell types as well as proliferative cells. In the immune cell cluster, both myeloid and lymphoid lineage cells were identified, of which uterine NK-cells (uNK) and macrophages (uM) were the largest populations. Several differentially expressed genes (DEGs) of the epithelial subtypes, uNKs, uMs and stromal cells were identified in women with PCOS compared with controls. DEGs between PCOS cases and controls were enriched in pathways related to cilium organization in the ciliated epithelium, extracellular matrix structure in stromal cells, and cysteine-type endopeptidase activity in uM. Of note, both 16 weeks of treatment with metformin and lifestyle management restored multiple DEGs in each subtype. This rigorous mapping of the human PCOS endometrium improves our understanding of cellular complexity and specific cell types. It provides new mechanistic insights into disease-specific endometrial dysfunction(s), and several of the identified dysfunctions can be reversed by current first-line interventions.

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RC11.4

Treatment with osilodrostat in ACTH-independent Cushing's syndrome

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Introduction
Cushing's disease (CD) is the most common cause of hypercortisolism. Therefore, the majority of studies focused on the efficacy and safety of novel steroidogenesis inhibitors included CD patients only. This is exactly the case with osilodrostat – new potent inhibitor of 11β-hydroxylase. However, approximately 10% of hypercortisolism result from cortisol-secreting adrenal adenoma. Data on potential differences in the treatment with osilodrostat between CD and Cushing's syndrome of adrenal origin (ACS) are lacking.
Aim
Hereby, we presents two patients with ACS, in whom, the response and doses of osilodrostat were different from CS patients regardless whether the CS patients were treated in our centre or described in the literature.
Cases:
Case 1
A 55-year-old women with cortisol secreting left adrenal adenoma, with UFC 2× upper normal limit (UNL). Decompensated diabetes mellitus and hypertension were contraindications for surgery. Osilodrostat was started with a dose of 2 mg/day and gradually increased to 8 mg/day with – surprisingly – simultaneous increase in UFC to 10 × UNL, severe deterioration of hypertension and life-threatening hypokalaemia of 2.1 mmol/l, despite active potassium supplementation. Due to the extremely high hypercortisolism, the dose was increased by 5 mg every two days up to 45 mg, with gradual decrease of cortisol level and UFC normalisation with the dose of 45 mg/day.
Case 2
A 45-year-old women with ACS and UFC 5 × UNL, was treated with osilodrostat, starting from 2 mg/day and increasing by 2 mg/day every day, and then, from the dose of 10 mg/day, increasing by 5 mg every other day, with no cortisol reduction up to the dose of 20 mg/day. The dose was escalated up to 45 mg/day, and after a week of treatment UFC normalisation was reached. No side effects was observed, no potassium supplementation was required.
Conclusions
1. Doses of osilodrostat required for ACS are usually much higher than those in CD.
2. Dose acceleration can be faster and the risk of overdosing and later necessity of dose reduction is low
3. Low initial doses can be ineffective or can even cause exacerbation of hypercortisolism
4. Typical dose which allowed to safe adrenalectomy with UFC slightly below upper normal limit was 45 mg/day
5. Side effects of osilodrostat can be rapid with severe hypokalaemia even despite active potassium supplementation or can be totally absent with potassium level above 4.0 mmol/l without any supplementation. Therefore, cloSemonitoring of potential side effects is mandatory.

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RC11.5

Pregnancy after bariatric surgery – Experience from a tertiary hospital

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Introduction
Maternal obesity is associated with an increased risk of gestational diabetes, large for gestational age (LGA) newborns, preterm delivery, congenital malformations, and fetal death. On the other hand, bariatric surgery before pregnancy is associated with a reduction of obesity-associated complications, but also with an increased risk of small for gestational age (SGA) newborns, fetal growth restriction and micronutrient deficiencies during pregnancy.
Aim
To evaluate the effect of bariatric surgery on maternal and fetal outcomes.
Methods
This was a retrospective observational study that included pregnant women followed by a multidisciplinary obesity team in a tertiary hospital, from September 2019 to March 2022. Participants were included in one of two groups:

(1) women with a history of gastric bypass or sleeve gastrectomy before pregnancy ($n=83$); (2) women with BMI$\geq$35 kg/m^2, without a history of bariatric surgery ($n=166$). Participants with loss of follow-up were excluded. Medical files were review for demographic and clinical data. Statistical analysis was performed using IBM SPSS Statistics 27. Multivariate analysis was performed to adjust for the following confounders: BMI prior to surgery in group (1) and BMI prior to pregnancy in group (2), maternal age, smoking during pregnancy, and history of thyroid dysfunction or essential hypertension.

Results

After adjusting for confounders, pregnancy after bariatric surgery was associated with higher gestational weight gain (10.97$\pm$7.08 vs 7.21$\pm$5.95, $\beta=0.294$, $P<0.001$), newborns with lower weigh percentile (36.85$\pm$20.93 vs 48.47$\pm$27.90, $\beta=-13.327$, $P<0.001$), an increased risk of iron deficiency (81.8% vs 67.2%, OR 2.480, $P=0.013$) and vitamin B12 deficiency (44.0% vs 24.4%, OR 2.357, $P=0.016$), and lower rates of gestational diabetes (16.9% vs 32.5%, OR 0.359, $P=0.003$), and cesarian section (22.9% vs 34.7%, OR 0,518, $P=0.044$). No statistically significant differences were observed between groups regarding preterm delivery (12.0% vs 6.0%, OR 2.422, $P=0.083$), gestational hypertension (4.8% vs 9.6%, OR 1.573, $P=0.608$), preeclampsia (2.4% vs 7.2%, OR 0.545, $P=0.548$) or fetal growth restriction (4.8% vs 0.6%, OR 11.247, $P=0.062$).

Conclusion

Pregnancy after bariatric surgery was associated with a lower risk of gestational diabetes and cesarian section, and a higher risk of micronutrient deficiencies. Risks and benefits of bariatric surgery before pregnancy must be considered in the decision making of obesity treatment in women of fertile age.

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RC11.6

Prognostic parameters of adrenocortical carcinoma. Single-centre confirmatory study of GRAS and S-GRAS scoring systems

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Introduction

Adrenocortical carcinoma (ACC) is a rare disease with a poor prognosis. In recent years, two prognostic scoring systems incorporating relevant clinicopathological features of ACC (ENSAT stage, grade, resection status, age at diagnosis, tumour symptoms) have been proposed: the GRAS and S-GRAS scoring systems. The prognostic value of these systems has been demonstrated in large, multicentre studies.

Aim

To su mmarize the clinicopathological features of ACC patients treated in our centre, to determine the individual prognostic value of each feature, and to compare these values with the prognostic value of the calculated GRAS and S-GRAS scores, and thus to validate them on a single-centre patient population.

Methods

For our retrospective study, we used data from 86 patients with ACC treated at Semmelweis University, Hungary between 01/01/2000 and 31/08/2022. Descriptive statistical methods were used to su mmarize clinicopathological characteristics. To determine the correlation of data with survival, we performed Kaplan-Meier survival analysis using a log-rank test and univariate Cox regression. For statistical calculations, $P<0.05$ was considered significant.

Results

The mean age of the patients at diagnosis was 50.9$\pm$15.21 years. At baseline, the most frequent clinicopathological features were ENSAT stage IV ($n=33$), R0 resection status ($n=34$) and cortisol excess ($n=48$). Of the parameters studied, a significantly increased risk of mortality was associated with cortisol excess (RR=2.87 $P<0.001$), higher (III-IV) ENSAT stage (RR=2.2, $P=0.002$), R1/2 resection status (RR=2.42, $P=0.001$) and Ki67 index above 10% (RR=3.82, $P=0.012$). Among the prognostic scores, a high GRAS score (3-4 points) (RR=2.6, $P<0.001$) and a high S-GRAS score (5-9 points, 7-9 points) (RR=2.47, $P<0.005$, RR=9.45, $P<0.001$) were associated with a higher risk of death.

Conclusions

Among the studied parameters, tumour grade, resection status, cortisol production and tumour stage could be considered independent prognostic factors. High GRAS and high S-GRAS scores were associated with poorer overall survival and increased mortality risk. The clinical applicability of these scoring systems is enhanced by the fact that their prognostic value was also confirmed in a single-centre study with a relatively low number of patients.

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Poster Presentations

Adrenal and Cardiovascular Endocrinology

P1

Crinecerfont (NBI-74788), a Novel CRF1 Receptor Antagonist, Lowers Adrenal Androgens and Precursors in Adolescents with Classic Congenital Adrenal Hyperplasia

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Introduction
Classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) is a rare autosomal recessive disorder characterized by deficiency of cortisol and oftentimes aldosterone, with elevated adrenocorticotropic hormone (ACTH) and steroid precursors that are shunted toward excess androgen production. A phase 2 study of adults with classic 21OHD demonstrated that crinecerfont–an oral, non-steroidal, selective corticotropin-releasing factor type 1 (CRF_1) receptor antagonist–substantially reduced elevated hormone markers after 14 days of treatment. The current study evaluated the effect of crinecerfont in adolescents with classic 21OHD, a population that may be especially challenging to manage due to the hormonal changes associated with puberty.
Methods
Eligible adolescents (14–17 years of age) with classic 21OHD received open-label crinecerfont (50 mg BID) for 14 days. Plasma ACTH and serum 17-hydroxyprogesterone (17OHP), androstenedione, and testosterone were assessed over 24 hours before (baseline) and after 14 days of crinecerfont treatment. For each participant, morning window values were calculated by averaging the samples collected at 0700h and 1000h (before morning glucocorticoid dose). Participants' glucocorticoid and fludrocortisone regimens were maintained during crinecerfont treatment.
Results
Eight participants (3 males, 5 females, ages 14-16 years) were included for analyses. At baseline, median morning window hormone concentrations were as follows: ACTH (226.2 pg/mL); 17OHP (7703.7 ng/dL); androstenedione (367.9 ng/dL); and in females, testosterone (63.5 ng/dL). At Day 14, median percent reductions in these parameters were as follows: ACTH (-57.1%); 17OHP (-69.5%); androstenedione (58.3%); and in females, testosterone (-76.2%). A $\geq$50% reduction from baseline to Day 14 in ACTH, 17OHP, and androstenedione was observed in 62.5%, 75.0%, and 50.0% of participants, respectively. Furthermore, 67% (2/3) of males with elevated androstenedione/-testosterone ratios ($\geq$0.5) at baseline achieved normal ratios ($<$0.5) at Day 14. Twelve treatment-emergent adverse events (TEAEs) were reported, with the most common being headache ($n=2$). Per investigator judgement, all TEAEs were mild and the majority were unrelated to study treatment. There were no serious AEs, discontinuations due to AEs, or safety concerns related to routine laboratory tests, vital signs, or electrocardiograms.
Conclusions
In adolescents with classic 21OHD, substantial median reductions (57-76%) in adrenal androgens and androgen precursors were observed after 14 days of crinecerfont treatment, consistent with results from a similar study of adults with classic 21OHD. Further studies are warranted to evaluate whether longer-term treatment with crinecerfont can allow for lower, more physiologic glucocorticoid dosing, consequently improving clinical outcomes such as weight, metabolic risk, growth/development, and fertility.

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P2

Pivotal Role of miRNAs during Establishment of the Mineralocorticoid Signaling Pathway and Kidney Development

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The Mineralocorticoid Receptor (MR, *NR3C2*) mediates sodium-retaining action of aldosterone. Recently, we have shown that the physiological sodium loss observed in newborns in their first days of life is due to a low renal MR expression. However, the underlying molecular mechanisms remain unknown to date. In the adult renal KC3AC1 cell line, we demonstrated that variations in extracellular tonicity, which exist in the nephron, modulate MR expression by posttranscriptional mechanisms involving recruitment of microRNAs (miRNAs) such as miR-30c-2-3p and miR-324-5p. These posttranscriptional regulators can bind to the 3'-untranslated (3'-UTR) region of target mRNA to modulate their stability and/or translation. Thus, we hypothesize that these same mechanisms may be responsible for the modulation of renal MR expression in the perinatal period, where variations in tonicity are observed due to the transition from intra-amniotic to extra-uterine life. Using primary culture of renal epithelial cells from neonatal mouse kidneys, harvested at day of birth (D0) and at Day 8 postnatal (D8), we showed that only miR-30c-2-3p regulates MR expression at D8. Therefore, we performed a complete transcriptomic analysis (RNA-Seq and miRNA-Seq) of kidneys collected at D0 and D8 to identify all miRNAs specifically involved in the regulation of MR expression in the perinatal period. To identify all the deregulated miRNAs and transcripts and to specify their involvement in biological processes and signaling pathways, we performed a comprehensive bioinformatics analysis. Then, we mainly focused on deregulated miRNAs that could modulate MR expression and affect mineralocorticoid signaling pathway. miR-Sequecing enabled us to identify 221 differentially expressed miRNAs. We first selected 3 underexpressed (miR-30a-5p, miR-30e-5p, and miR-802-5p) and 3 overexpressed (miR-431-5p, miR-409-3p, and miR-92a-1-5p) candidate miRNAs (FDR $<$ 0.05 and log2FC$>$1) having putative binding sites in MR 3'-UTR. Paradoxically, our results showed that over-expression of miR-30a-5p, miR-30e-5p, or miR-802-5p increased MR expression (from 50 to 100%, $P<0.05$) at D0, suggesting that these miRNAs could either positively modulate MR expression during renal development or involve an intermediate factor. Conversely, overexpression of miR-92a-1-5p, miR-431-5p, and miR-409-3p at D8 induced a decrease (from 30-40%, $P<0.05$) in MR expression, suggesting that these miRNAs could also modulate MR expression in the postnatal period. Currently, we are evaluating whether these miRNAs could be used as severity or prognostic biomarkers of sodium loss in neonates by quantifying their expression in urinary exosomes of preterm and term infants with the goal to better understand molecular mechanisms regulating MR expression in the perinatal period.

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P3

Late onset congenital adrenal hyperplasia after the fifth decade of life: case series

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Introduction
Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder that is caused by mutations of genes involved with adrenal steroidogenesis. The mutations mostly occur in the 21-hydroxylase gene and rarely in the 3β-hydroxysteroid dehydrogenase gene or 11β-hydroxylase genes. Our aim is to present a series of 3 cases of patients with late onset CAH, probably due to 21-hydroxylase deficiency, after 50 years of age.
Case series
Patient 1 - The first patient was initially diagnosed with a 6.4/4.5 cm right adrenal adenoma and left micronodular adrenal hyperplasia. He underwent right adrenalectomy due to the large size of right adrenal adenoma. After surgery the lab tests showed: low serum cortisol; ACTH = 2000 pg/ml (3-66); very high LH, FSH and progesterone; normal DHEAs; testosterone = 3.06 ng/ml (1.75-7.81); basal 17-hydroxyprogesterone = 254 ng/ml; 17-hydroxyprogesterone 1h after administration of ACTH = 1154 ng/ml. After the diagnosis was established, the patient was treated with Prednisone and Fludrocortisone. Patient 2 - The patient was diagnosed with hypospadias at the age of 3 for which he underwent multiple surgeries, which has only recently been corrected. He presented to our department after having a pelvis MRI which detected the presence of a hypoplastic uterus, vagina (opening to the urethra), ovaries and a hypoplastic prostate. The abdominal CT showed right macronodular adrenal hyperplasia and left micronodular adrenal hyperplasia. He had very high LH, FSH and progesterone; normal DHEAs; testosterone = 1.71 ng/ml (1.75-7.81); basal 17-hydroxyprogesterone = 720

ng/ml; 17-hydroxyprogesterone 1h after administration of ACTH = 1320 ng/ml. Unlike the first patient the lab tests showed minimal adrenal insufficiency, therefore this patient did not require glucocorticoid and mineralocorticoid replacement. Patient 3 - This patient presented hypospadias in the first years of life similar the second patient. He had bilateral macronodular adrenal hyperplasia with minimal adrenal insufficiency; high progesterone; basal basal 17-hydroxyprogesterone = 36 ng/ml; 17-hydroxyprogesterone 1h after administration of ACTH = 1002 ng/ml; testosterone = 1.52 ng/ml (1.75-7.81). The mean age at diagnosis for these patients was 53.3 years. The karyotype of these patients was 46XX. On clinical examination all three patients had missing testicles in the scrotum and hypoplastic penis.
Conclusion
Although CAH is a very rare condition, the clinical signs and lab tests leading to the diagnosis of these three patients were different and polymorphic. The diagnosis after the fifth decade of life of these 46 XX patients with congenital adrenal hyperplasia has numerous psychosocial implications, as they have a male gender identity.

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P4

Hypogonadism in men with congenital adrenal hyperplasia. A retrospective longitudinal analysis with a special focus on testicular adrenal rest tumors and 11-oxygenated androgens

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Background
Hypogonadism is frequent in men with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD). It has recently been demonstrated that testicular adrenal rest tumors (TART) are a source of 11-oxygenated androgens that might impair testicular function, in addition to their local compressive effects. Data on long-term course of testicular function in men with 21OHD and the role of potential influential factors such as presence of TART and 11-oxygenated androgen formation is sparse.
Methods
Retrospective single-center study in 30 men with classic 21OHD ($n = 11$ with TART, $n = 16$ without TART, $n = 3$ unknown). Median age at baseline was 31.0 years (IQR 26-38). The median observation period was 12 years (IQR 8-13). Levels of testosterone (T), 17-hydroxyprogesterone (17-OHP), androstenedione (A4) and 11-oxygenated androgens were measured simultaneously by LC-MS/MS.
Results
On average, 43.2% (No TART) and 54.6% (TART) of all T measurements in each individual patient were below the reference range (n.s.) with gonadotropin levels being inappropriately normal or suppressed in most patients. In multivariate mixed model analysis, including age, BMI, type of glucocorticoid (GC), GC-equivalence dosage and phenotype, T levels were comparable between men with and without TART. T levels remained stable during the observation period in men without TART (Baseline 11.37 $\pm$ 1.52 nmol/l, last visit 12.1 $\pm$ 2.1 nmol/l) and increased in those with TART (Baseline 9.48 $\pm$ 1.68 vs. last visit 14.9 $\pm$ 2.3 nmol/l ($P = 0.006$). At baseline, the A4/T-ratio was significantly higher in men with TART (1.39 $\pm$ 1.63) than in those without (0.27 $\pm$ 1.63), and there was a Time*Group interaction, indicating a decrease in the A4/T-ratio in men with TART ($P = 0.04$). This resulted in a trend for the A/T-ratio being higher in men with TART (0.5 $\pm$ 1.6 vs 0.3 $\pm$ 1.5; $P = 0.057$) across the whole observation period. 11-ketotestosterone levels were higher in men with TART (1.8 $\pm$ 0.006 nmol/l) than in men without TART (0.68 $\pm$ 0.006 nmol/l) but remained unchanged over time in both groups.
Conclusion
A normal serum T does not exclude hypogonadotropic hypogonadism in men with 21OHD, which is a common problem that appears to remain stable in the long run. The presence of TART does not have a negative effect on T-levels. In contrast, the detection of TART should prompt further assessment, including A4, gonadotropins, and 11-ketotestosterone, followed by treatment optimization to improve gonadal T production.

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P5

Catestatin is associated with the impairment of carbohydrate metabolism

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Background
Arterial hypertension (AH) and 2 type diabetes mellitus (2TDM) are the critical risk factors for the development of cardiovascular diseases. Catestatin (CTS) is known as a marker of AH via its antiadrenergic and vasodilating actions, but also can improve insulin sensitivity.
Objective
To investigate the relations between CTS levels and parameters of carbohydrate metabolism in patients with AH, including AH with 2TDM, and establish the prognostic potential of CTS among this population of patients.
Materials and Methods
The present study was designed as a single-center cross-sectional study and performed in accordance with all ethical principles of the Helsinki Declaration. The study protocol was approved by the local ethics committee. Each study participant signed a written informed consent prior to any protocol procedures. We enrolled in the study 136 subjects, moreover, 106 of them had primary AH and 30 are healthy volunteers. Furthermore, 51 hypertensive patients have comorbid 2TDM. The diagnosis of AH was established according to the 2018 ESC/ESH guidelines for the management of AH. The diagnosis of 2TDM was determined according to the 2022 ADA Standards of Medical Care in Diabetes. The clinical examination and medical history data, as well as blood samples, were collected at the screening visit. The routine biochemistry parameters were analyzed on the same day. The plasma samples for CTS determinations were stored at -80°C for later analysis. Plasma CTS levels were measured by an enzyme-linked immunosorbent assay (ELISA), using a commercial kit (E4996Hu, BT Lab, Shanghai, China) according to the manufacturer's instructions. The data were presented as a mean $\pm$ SD. Statistical significance was defined as $P < 0,05$. Statistical data were analyzed using SPSS statistical software (SPSS 25.0 for Windows, IBM, Armonk, NY, USA).
Results
The mean CTS concentration was 5,38 $\pm$ 1,22 ng/ml. CTS plasma levels were significantly lower in patients with AH in comparison with control subjects (5,02 $\pm$ 1,09 vs. 6,64 $\pm$ 0,72 ng/ml; $P < 0,001$). Moreover, the patient with AH and 2TDM had significantly decreased CTS levels compared with the hypertensive patient without 2TDM (4,47 $\pm$ 1,16 vs. 5,61 $\pm$ 0,61ng/ml; $P < 0,001$). CTS significantly negatively correlated with such characteristics of carbohydrate metabolism as insulin ($r = -0,382$; $P < 0,001$), glucose ($r = -0,45$; $P < 0,001$), index HOMA-IR ($r = -0,481$; $P < 0,001$), and HbA1c ($r = -0,525$; $P < 0,001$).
Conclusions
In this study, we established the negative associations between CTS levels and parameters of carbohydrate metabolism, which allows us to consider CTS as a predictor of the development of 2TDM and determines its future diagnostic potential for both AH and 2TDM.

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P6

Patients with NF1 need routine hormonal screening towards pheochromocytoma

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Up to 40% of pheochromocytoma cases have a genetic background. The prevalence of pheochromocytoma in neurofibromatosis type 1 (NF1) was reported to be from 0.1 to 5.7%. However, the actual incidence of pheochromocytoma in NF1 seems to be underestimated. Current recommendations on NF1 do not include systematic biochemical screening for the presence of pheochromocytoma. Our aim was to analyse clinicopathological characteristics of pheochromocytoma in the course of NF1 syndrome with additional comparison to non-NF1 cases. We performed a database search for pheochromocytoma patients, diagnosed and treated in Endocrinology Department, University Hospital in Cracow from 2005 to 2022. In the group of 183 patients with histologically confirmed pheochromocytoma, 8 cases with NF1 were identified (4.4%). The group of NF1 patients comprise 4 men and 4 women. Median patient's age was 44 years (range: 29-70 years). Most cases were diagnosed incidentally (6/7). The most common manifestation of the disease was

hypertension (5/8). In majority of patients (6/8), NF1 diagnosis was stated based on clinical picture, in two cases genetic testing was performed. The median size of the tumour was 4.2 cm (range: 2.4-10.8 cm). In all cases with preoperative 68Ga DOTATATE PET/CT imaging (3/8), pathological tracer uptake was seen. 24-hour urinary fractionated metanephrines were significantly elevated in 6 cases. One patient had aggressive, metastatic tumour, which subsequently led to patient's death, the rest of patients remained disease-free during follow-up (median time: 44.5 months). One patient had synchronous bilateral disease. In three cases, accompanying neoplasms from different origin were observed (adrenocortical carcinoma, prostate cancer, GIST of the jejunum). PASS score was defined in 6 patients - in majority of cases it exceeded 3 (range 4-10). In 4 subjects, histopathological examination revealed composite pheochromocytoma with ganglioneuroma component. There were no significant differences between NF1 and non NF1 pheochromocytomas regarding sex, age, tumour size, PASS score, levels of metanephrines. In patients with NF1, composite pheochromocytoma was diagnosed much more often than in non-NF1 cases (with p value = 0.003). Pheochromocytoma in the course of NF1 is very often diagnosed incidentally. Most commonly it is manifested by hypertension, which could be easily overlooked. Sometimes it could metastasize, leading to patient's death. A routine hormonal assessment towards pheochromocytoma in patients with NF1 may improve patient's safety and treatment outcomes. NF1 should be excluded in all cases with composite pheochromocytoma, since this type of tumour is more commonly diagnosed in NF1 patients.

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P7

Treatment compliance affects the reliability of clinically and biochemically important variables used for the titration of mineralocorticoid treatment in primary adrenal insufficiency

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Background
There is currently no agreed consensus for the optimization and titration of mineralocorticoid (MC) therapy in patients with primary adrenal insufficiency (PAI).
Objective
To measure serum (sFC) and urine (uFC) fludrocortisone levels and explore their relationship with biochemically and clinically important variables (including treatment compliance) in order to evaluate their usefulness as markers to guide the MC replacement titration.
Methods
Multi-centre, observational, cross-sectional study on 41 patients (median age 39 years, IQR 27-56) with PAI on MC replacement therapy (median dose 100 mg/d, range 50-400). sFC and uFC levels (measured by LC-MS/MS), plasma renin concentration (PRC), electrolytes (Na^+, K^+), mean arterial blood pressure (MAP), total daily Glucocorticoid (dGC, hydrocortisone equivalents) and MC (dMC) dose, anthropometrics and assessment of GC and MC treatment compliance were incorporated into statistical models.
Results
We observed a close relationship between sFC and uFC ($r=0.434$, $P=0.005$) as well as between sFC and the time from the last FC dose ($r=-0.355$, $P=0.023$). Total daily MC dose was related to dGC dose ($r=0.556$, $P<0.001$), K^+ ($r=-0.388$, $P=0.013$) as well as sFC ($r=0.356$, $P=0.022$) and uFC ($r=0.531$, $P<0.001$) levels. PRC was related to Na^+ levels ($r=0.517$, $P<0.001$) and MAP ($r=-0.427$, $P=0.006$), but not to MC dose, sFC or uFC . Multiple linear regression analyses did not support a role for sFC, uFC or PRC measurements and confirmed K^+ ($B=-44.593$, $p=0.005$) as the most important variable to guide dMC titration. However, when compliance was inserted into the model, it was the only factor affecting dMC.
Conclusions
sFC and uFC levels are not helpful in dMC titration in PAI. Clinicians should continue to rely on clinical and biochemical important variables (electrolytes, blood pressures and symptoms) to guide their decisions on MC dose adjustment, being aware that patient's compliance to treatment is a major contributor for the reliability of such clinical markers.

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P8

SARS-CoV-2 provoked acute adrenal crisis with severe hypovolaemic hyponatraemia

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Hyponatraemia is the commonest electrolyte disturbance among inpatients. Prompt diagnosis and management of the underlying cause is important. A 49-year-old Caucasian male presented to the emergency department with a two-day history of fever, altered mental status, vomiting, diarrhoea and postural dizziness. A rapid point of care RT-PCR test resulted positive for the SARS-CoV-2. A provisional diagnosis was presented of COVID-19 encephalopathy. The patient was usually fit and well, worked as a heating engineer and had no known immunodeficiency. Medical history was notable for atypical polymyalgia rheumatica treated with oral glucocorticoids more than two years prior. Admission laboratory studies were significant for a serum sodium level of 130mmol/l. Despite supportive treatment and with normal saline his clinical condition deteriorated over the first seventy-two hours of admission culminating in orthostatic syncope during clinical examination on day three. Repeat laboratory testing revealed serum sodium had fallen to 118 mmol/l. Urine sodium and osmolality were high. Random cortisol was reported as 6 nmol/l. Following intravenous resuscitation with high dose glucocorticoids and hypertonic saline his condition improved with slow normalisation of serum sodium, restoration of extracellular fluid volume and abatement of orthostatic symptoms. A tetracosactide stimulation test was performed with t = 0 min cortisol level of 9nmol/l and t = 30 min 39 nmol with a pre-test serum ACTH level of 4ng/L. A t = 60 min cortisol was not performed. The remainder of the pituitary profile including serum thyroid stimulating hormone was unremarkable. Magnetic resonance (MR) imaging of the Sella revealed no evidence of pituitary adenoma and subsequent MR adrenals showed bilateral adrenal atrophy. Lumbar puncture revealed quiet cerebrospinal fluid. Adrenal antibodies were not available at the time of writing. The patient was discharged on oral hydrocortisone and remains well at three months follow up. The presumptive diagnosis in this case is acute SARS-CoV-2 infection precipitating acute adrenal crisis in a predisposed individual. The unexpectedly low plasma ACTH was surmised to be due to acute illness. The patient awaits formal endocrinological evaluation. This case highlights the importance of prompt diagnosis and expedient management of hyponatraemia and particularly in high stakes cases where the underlying mechanism is adrenal failure. Although an uncommon cause of hyponatraemia it is critical to exclude adrenal insufficiency when approaching such patients. Timely recognition of adrenal crisis is associated with reduced complications and mortality associated with this disease.

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P9

Determination of dexamethasone level by liquid chromatography with tandem mass spectrometry after low-dose dexamethasone suppression test

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Introduction
Low-dose dexamethasone suppression test is used to screen for excess cortisol production (Cushing's syndrome). It is recommended to use cut-off for suppression of serum cortisol (SC) < 50 nmol/l after 1 mg dexamehason suppression test (DST). Plasma dexamethasone levels are affected by many factors resulting in lower test specificity. Simultaneous analysis of dexamethasone and cortisol levels can improve diagnostic accuracy of DST. We used cut-off level of plasma dexamethasone > 3 nmol/l, which was validated in our previous study. The aim of the study was to detect the rate of false positive results by measuring plasma dexamethasone level after DST.

Methods
The prospective study of DST was carried out in 116 patients (71 female, 45 male) and 100 healthy controls (60 female and 40 male). The patients' cohort consisted of individuals with unilateral adrenal lesion ($n=28$), bilateral adrenal lesion ($n=30$), pituitary tumor ($n=21$) and clinically suspected Cushing's syndrome ($n=37$). Serum cortisol was determined by chemiluminescence immunoassay (Atellica Siemens). Plasma cortisol and dexamethason were determined by liquid chromatography with tandem mass spectrometry (2D-LC-MS/MS).
Results
Sixty-nine patients (59%) achieved SC <50 nmol/l. All of them had sufficient plasma dexamethasone level (>3 nmol/l). Forty-seven patients (41%) had SC >50 nmol/l, out of whom 44 achieved sufficient plasma dexamethasone levels while three did not. In this group of 47 patients further endocrinological examination ruled out hypercortisolism in 20 patients including 3 patients with insufficient dexamethasone levels and confirmed overt Cushing's syndrome in 16 patients. Eleven patients were found to have possible autonomous cortisol secretion. In the group of 100 healthy controls, SC <50 nmol/l was reached in 91 cases (91%). Nine individuals had SC >50 nmol/l, out of whom two patients had a level of plasma dexamethasone <3 nmol/l. In all nine individuals further endocrinological examination excluded hypercortisolism.
Conclusion
2D-LC/MS/MS is considered to be the golden standard in the analysis of both steroid hormones and dexamethasone. Insufficient plasma dexamethasone levels were found in 2% of subjects and were therefore the cause of false positivity of 1 mg dexamethasone suppression test. Simultaneous measurement of plasma dexamethasone and cortisol improved the specificity of DST. The results confirm that DST can be falsely positive even in healthy individuals with sufficient levels of dexamethasone.

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P10

Prevalence and incidence of type 2 diabetes mellitus in patients with adrenal incidentalomas: A study of 709 cases

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Aim
To evaluate the prevalence and incidence of type 2 diabetes in patients with nonfunctioning adrenal incidentalomas (NFAI) and autonomous cortisol secretion (ACS) coming from a cohort of adrenal incidentalomas consecutively evaluated in a tertiary hospital in a predefined period (2013-2020).
Methods
In this retrospective study, adrenal incidentalomas $\geq$1cm with ACS and NFAI were included. ACS was defined by a post-dexamethasone suppression test (DST) serum cortisol $\geq$1.8 µg/dl, in the absence of signs of hypercortisolism, and NFAI as a DST $<$1.8 µg/dl and no biochemical evidence of other hormonal hypersecretion.
Results
Inclusion criteria were met by 709 patients, 231 with ACS and 478 with NFAI. At the diagnosis of the adrenal incidentaloma, type 2 diabetes was present in in 172 (24.3%) patients, 13 were under treatment only with life-style changes (diet and exercise), 98 with oral antidiabetics, 16 with insulin in monotherapy and 45 with insulin and oral antidiabetic drugs in combination. No difference in its prevalence was found between patients with ACS and NFAI (27.7% vs. 22.6%, $P=0.137$). Neither in the proportion of type 2 diabetic patients under insulin therapy (33.9% vs. 23.1%, $P=0.130$). However, fasting plasma glucose and HbA1c levels were significantly higher in patients with ACS than with NFAI (112.3 ± 35.56 vs 105.0 ± 29.05 mg/dl, $P=0.004$ and 6.5 ± 1.36 vs. 6.1 ± 0.89%, $P=0.005$, respectively). Furthermore, patients with type 2 diabetes had higher urinary free cortisol (54.8 $\pm$101.52 vs. 38.3 ± 29.08 µg/dl; $P=0.039$) and late-night salivary cortisol levels (5.0 ± 5.73 vs. 3.5 ± 3.57 µg/dL, $P=0.010$) than those without type 2 diabetes. After a media follow-up of 28 months [IQR 2.0-125.3], a total of 24 patients developed type 2 diabetes. No differences in incidence were found between patients with ACS and NFAI (HR 1.17, 95% 0.52-2.64).
Conclusion
Type 2 diabetes affects a quarter of patients with adrenal incidentalomas, with no differences in its prevalence and incidence in patients with ACS and NFAI. However, the glycemic control seems to be worse in those who have associated ACS. Also, higher levels of urinary and salivary cortisol are found in patients with type 2 diabetes compared to those without type 2 diabetes.

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P11

Diagnostic accuracy of 18F-FDG PET/TC for the characterization of adrenal lesions in a heterogeneous population

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Purpose
Diagnosis of adrenal lesions requires hormonal investigation and morphological characterization; when CT and MRI imaging are equivocal, 18F-FDG-PET/CT could be a useful tool, although sensitivity and specificity varied among cohorts. The use of tumour-to-liver maximum standardized uptake values (SUVratio) was found to be accurate, but the best threshold value has not been identified yet. A SUVratio $>$ 1.5 was associated with malignancy with a good performance. The aim of the study was to evaluate the performance of the SUVratio $>$ 1.5 in our heterogenous population.
Patients and methods
Retrospective analysis of Endocrinology, Surgery and Oncological Units on patients who received care for adrenal lesions (2013-2022). The cohort was narrowed down to patients who underwent 18F-FDG-PET/CT to assess the risk of malignancy for adrenal nodules. Benignity was defined by histology or when the lesion remained stable or had a minimal increase in diameter ($<$20% and $<$5 mm) on the 12-month follow-up imaging. The performance of SUVratio $>$ 1.5 proposed and the optimal SUVratio in our population was calculated by ROC curves.
Results
177 patients with adrenal lesions were selected; of them, 36 underwent 18FDG-PET/CT and were included (17 M/19 F, age at diagnosis 61.2 $\pm$11.7 years); 6 patients had bilateral lesions, leading to a total of 42 adrenal lesions (diameter 36.1 $\pm$20.3 mm). Twenty-nine lesions were classified as benign, 11 as malignant and 2 as pheochromocytomas. Considering malignancies, 8 patients had adrenal metastases (2 of them bilateral) and 1 adrenocortical carcinoma (ACC). The diagnosis of adrenal masses with a SUVratio $>$ 1.5 was: 10 adrenal metastases, 1 ACC, 2 non-functioning adrenal adenomas, 1 adrenal hyperplasia and 1 pheochromocytoma. In the whole population, the SUVratio agreed with the diagnosis in 38 cases (90.5%); in the 4 discordant cases with a SUVratio $>$ 1.5 and non-malignant lesion, the diagnosis was: 2 non-functioning adenomas, 1 hyperplasia, and 1 pheochromocytoma. The SUVratio cut-off of 1.5 showed 100% Sn, 87% Sp, 73% PPV, and 100% NPV. The SUVratio cut-off calculated in our population was 1.55 (Sn 100%, Sp 73.7%, AUC 0.868), with similar values excluding both pheochromocytomas and metastases from the analysis (SUVratio cut-off 1.49, Sn 100%, Sp 96.3%, AUC 0.988).
Conclusion
18F-FDG PET/CT could help in decision making process avoiding unnecessary surgery. The SUVratio cut-off of 1.5 has a good performance in a heterogenous population with adrenal lesions.

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P12

HPA axis suppression in patients treated with glucocorticoids: relationship to dose, duration and likelihood of recovery

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Background
Tertiary adrenal insufficiency (TAI) is a complication of long-term exogenous steroid use which results in suppression of the hypothalamic-pituitary-adrenal (HPA) axis. The short synacthen test (SST) is used to assess HPA axis function and recovery during glucocorticoid weaning. This study examined the effect of steroid preparation, dosage and therapy duration on HPA axis suppression.
Method
A retrospective analysis of 950 SSTs performed between 2016 and 2021. Of these 950, 772 (81%) were first SSTs and 178 (19%) were repeat SSTs. Patients under investigation for TAI were identified ($n=$ 512) and included in the analysis, those with suspected primary or secondary adrenal insufficiency were excluded. Data

collected included patient demographics, details of steroid use and where available 9am cortisol, baseline ACTH and SST results.
Results
Of the 512 patients 35% failed the SST (peak cortisol <420 nmol/l, ROCHE GEN 2). 33% of those receiving oral steroids had evidence of TAI, compared to 22% and 6% of those receiving inhaled or topical monotherapy, respectively. Most at risk of HPA axis suppression were patients taking combination therapy of oral with either inhaled or topical steroids, with evidence of TAI in 44% and 41% respectively. No patients receiving both topical and inhaled steroids had evidence of TAI. Prednisolone equivalent dose did not differ significantly between those who passed or failed their SST (mean 5.39mg vs 6.01mg, $P = .54$). Total steroid duration was not a predictor of HPA axis recovery [recovery 63.7 months vs non recovery 70.5 months, $P = .64$]. 178 repeat SSTs were conducted in 125 patients who failed initial SST. The mean number of repeat SSTs in this cohort was 1.5 (SD 1.1, range 1-8). Overall, 34% of patients undergoing repeat SST demonstrated recovery of the HPA axis with a mean time to recovery of 13.2 months (SD 9.8, range 2.5-49).
Conclusion
Those most at risk of HPA axis suppression are groups on combination therapy of oral with either inhaled or topical preparations, this is of particular relevance to patients with conditions such as asthma or eczema where severe disease can often necessitate dual therapy. 67% of patients on oral steroids had no evidence of TAI. Mean prednisolone equivalent dose or steroid duration did not predict HPA axis recovery. 34% patients undergoing repeat SST testing demonstrated recovery of the HPA axis, indicating that with careful medication adjustment many patients can reverse a suppressed HPA axis.

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P13

Prolonged Adrenocortical Blockade Following Interruption of Osilodrostat in ACTH-dependent Cushing's syndrome

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Introduction
Osilodrostat is the newest approved steroidogenic inhibitor drug for the treatment of Cushing's syndrome (CS). In this presentation, we describe 3 patients who experienced an unexpectedly prolonged adrenal insufficiency following interruption of this treatment.
Methods
A monocentric retrospective analysis (October 2019 to January 2023) of ACTH-dependent CS patients controlled with Osilodrostat was performed to identify patients with proven adrenal blockade persisting at least 4 weeks after cessation of Osilodrostat. Hormonal evaluation included basal serum cortisol, and DHEA-S as well plasma ACTH, aldosterone and renin levels determination. Stimulation test results with ACTH 250mcg and CRH 100mcg injection were also analyzed, when available.
Results
We identified 25 CS patients controlled by Osilodrostat and 5 among them experienced an unplanned treatment interruption due to adverse events or drug intolerance. Persistence of adrenocortical blockade was observed in 3 of those patients and lasted from 6 weeks to 9 months depending on cases. The reasons for Osilodrostat interruption were either a skin eruption (case 1) or a severe adrenal insufficiency secondary to infectious episodes (cases 2 and 3), requiring mineralocorticoid supplementation in the most acutely ill patient (case 3). Osilodrostat daily doses were 2, 4 and 10 mg/day at the time of interruption, respectively. Total Osilodrostat treatment duration before cessation did not seem to predict the severity of this outcome. On their latest hormonal evaluation, every patient showed an insufficient serum cortisol peak response to ACTH stimulation test, although 2/3 patients had a normal basal cortisol serum value > 250 mmol/l. Basal ACTH was high (>13 pmol/l) in the 3 patients. DHEA-S values were suppressed in all cases under Osilodrostat treatment and remained low during all the follow-up duration after cessation. At the latest available follow-up, Fludrocortisone supplementation was still necessary in the patient with mineralocorticoid deficit (case 3). CRH test was performed in 2 patients showing a significant response of ACTH but not of cortisol.
Conclusion
The duration of adrenal blockade in these 3 patients is hardly explained by the drug's half-life (~4h) and remains to be elucidated. Additional research is also needed to identify predictors of this long-term effect on adrenal function. This highlights the importance of monitoring adrenal function and preventing adrenal crisis in patients at risk even after Osilodrostat interruption.

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P14

Opioid Use and Adrenal Insufficiency in Olmsted County, MN, USA: A Population-Based Study

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Background
Chronic opioid use may lead to adrenal insufficiency (AI) due to suppression of the hypothalamic-pituitary-adrenal axis. We aimed to determine incidence of AI and mortality in patients treated with chronic opioid therapy in a standardized geographically well-defined population.
Methods
In this population-based cohort study we assessed the standardized incidence rate of first time met chronic opioid use and adrenal insufficiency in adult residents of Olmsted County, MN, USA, from January 1, 2005, to December 31, 2021. The Rochester Epidemiology Project was used as a database since it links medical records for all patients in Olmsted County since 1966. Incidence rates were standardized for age and sex according to the 2020 US white population. Chronic opioid use was defined as opioid therapy for at least 3 months of consecutive use of either transdermal fentanyl or oral opioids based on prescription database. AI was defined based on presence of chronic ($\geq$ 6 months) glucocorticoid therapy. Elixhauser morbidity index was used.
Findings
Between 2005 and 2021, 8359 patients (mean age 60.8 years, 60% women) were identified to have chronic opioid use. Standardized incidence rates for chronic opioid use decreased from 533 (95% Confidence Interval, CI 484-583) per 100 000 person-years in 2005 to 138 (95% CI 116-159) in 2021. After 15 years of follow-up and adjusting for the competing risk of death, an estimated 11.3% (95% CI 10.4-12.3%) of patients treated with chronic opioids met criteria for AI at a mean age of 64.8 years (61% women). When compared to referent subjects, and after adjusting for age, sex, prior hospitalizations, morbidity index, and year of index date, patients on chronic opioids were at higher risk to be diagnosed with AI (Hazard ratio, HR of 2.2, 95% CI 1.9-2.6). When compared to referent subjects, and after adjusting for morbidity index, history of hospitalizations, age, and sex, and AI, patients treated with opioids had a higher mortality (HR 1.74, 95% CI 1.61-1.87). Diagnosis of AI was independent predictor of mortality in patients treated with chronic opioids (HR 2.27, 95% CI 2-2.58).
Interpretation
We show a decrease in chronic opioid use between 2005 and 2021. Patients treated with chronic opioids demonstrated a 11.3% of cumulative incidence of AI. Patients treated with chronic opioids and concomitant AI had higher mortality even after adjusting for morbidity and prior hospitalizations.

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P15

Neonatal endotoxin exposure alters glucocorticoid levels in lymphoid organs of adult mice

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The neonatal immune system is not fully developed, making neonates more susceptible to early-life infection. Early-life activation of the immune system has lasting implications for health and disease. Glucocorticoids (GCs) are steroid hormones that modulate the immune response and increase in response to immune activation. GCs are produced by the adrenal glands and also by lymphoid organs (e.g., bone marrow, thymus, spleen). In neonatal mice, GC levels increase acutely in blood and lymphoid organs in response to the endotoxin, lipopolysaccharide (LPS, derived from *E. coli*). Yet, it is not known how early-life LPS exposure affects lymphoid organ GC levels in adulthood. We assessed whether LPS administration during the neonatal period ('first hit') in mice affects GC regulation in blood and lymphoid organs in adulthood when challenged again with LPS ('second hit'). We administered LPS (50 μg/kg i.p.) or saline (vehicle control) to male and female

C57BL/6J neonatal mice at post-natal day (PND) 4 and 6. We further split the mice into two groups and administered LPS (50 μg/kg i.p.) or saline in adulthood (PND90) (2x2 design). 4 hr after LPS administration at PND90, we collected whole blood, bone marrow, thymus, and spleen. We bisected the tissues and measured a panel of 10 steroids via liquid chromatography tandem mass spectrometry (LC-MS/MS) and transcripts of key steroidogenic enzymes (*Cyp11b1*, *Hsd11b1*, *Hsd11b2*), GC receptor (GR), and mineralocorticoid receptor (MR) via RT-qPCR. Neonatal LPS treatment altered LPS-stimulated, but not baseline, GC levels in adult mice. Specifically, neonatal LPS treatment increased lymphoid, but not blood, levels of corticosterone (main active GC in mice) and 11-dehydrocorticosterone (corticosterone metabolite) in LPS-treated males, but not females. Transcripts of key steroidogenic enzymes were present in all lymphoid organs, and there were effects of neonatal treatment in LPS-treated adults for some transcripts. Transcripts of GR and MR were present in all lymphoid organs, and neonatal LPS treatment decreased GR and MR transcript levels in the spleen of LPS-treated males and females. These results suggest that LPS exposure during early life has long-term effects on GC signaling in lymphoid organs. Importantly, these data demonstrate that lymphoid organs modulate local GC levels independently of circulating GC levels. Local GC production is a potential mechanism by which early-life bacterial infections can exert long-lasting programming effects on the immune system.

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P16

Immunophenotypic differences in patients with primary adrenal insufficiency of different etiology

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Background
Primary adrenal insufficiency (PAI) has been associated with increased risk of infection, adrenal crises and a higher mortality rate. This is caused by altered circadian cortisol profiles, which ultimately lead to immune cell dysregulation. In this study, we aim to characterize differences in immunophenotype of PAI patients of three different etiologies.
Methods
Cross-sectional single center study including 28 patients with congenital adrenal hyperplasia (CAH), 27 patients after bilateral adrenalectomy due to Cushing's syndrome (BADx), 21 patients with Addison's disease (AD) – all substituted with a stable daily median dose of 25 mg hydrocortisone (IQR 5 mg for BADx and AD and IQR 10 mg for CAH) – and 52 healthy controls. Peripheral blood mononuclear cells were isolated and used for analysis of immune cell subsets using multicolor flow cytometry after four-hour stimulation with phorbol myristate acetate (PMA)/Ionomycin, as well as a K562 based natural killer (NK-) cell cytotoxicity assay and qPCR analysis of clock gene expression.
Results
The percentage of IFNγ-secreting T helper (Th1) in AD ($P=0.0024$) and cytotoxic (Tc1) cells in CAH ($P=0.0055$) and AD patients ($P=0.0075$) was significantly reduced compared to controls. We additionally observed a downregulation of the percentage of IL-4$^+$ Th2 cells in AD patients ($P=0.0157$) and Tc2 cells in AD ($P=0.0154$) and CAH patients ($P=0.0012$) compared controls. IL-17 producing T-cells were also downregulated in patients with AD compared to the other patient groups and controls ($P<0.0001$). NK-cell cytotoxicity (NKCC) was reduced in all subsets of PAI patients compared to controls with the smallest change in patients with CAH (mean specific lysis 57.5% in controls, 21.7% in CAH, -0.5% in AD and -28.7 in BADx). Activated NK-cell percentages were upregulated in BADx ($P=0.0008$) and AD patients ($P=0.0348$) compared to controls, also expressed as an increase in degranulation marker CD107a expression (BADx $P<0.0001$; AD $P=0.0002$). In contrast to NK-cell activating receptors, expression percentage of NK-cell inhibiting receptor CD94 was upregulated in both BADx and AD patients ($P<0.0001$).
Conclusion
This study presents novel data on immunophenotypic differences in subsets of PAI of differential etiology. Further analysis of potential influencing factors of immune regulation is necessary to determine the impact of imprinting effects of long-term GC excess and effects of elevated glucocorticoid and androgen precursors or 11oxC19 concentrations.

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P17

What are the lived experiences of family and carers for adults during an acute episode of adrenal crisis: A qualitative analysis using focus group interview

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Purpose
To gain an understanding of lived experiences of the role of family and carers during an acute episode of adrenal crisis through qualitative interviews with family carers. To gain an understanding of the role of family members and cares during an acute episode and to make recommendations for future standards of care in supporting family and carers to support self-management for loved ones, and health care professionals.
Methods
This study used the Braun and Clarke's 2006 approach to thematic analysis to explore qualitative data derived from five focus-group interviews to investigate the impact of Adrenal Insufficiency (AI) on family members and carers. Stratified by Adrenal Insufficiency type and country of residence in depth interviews were conducted to gain insight and understanding of the barriers and enablers to adherence, self-management to treatment, preventative strategies to minimise the risk of AC, and the provision of patient education and care services during the COVID – 19 Pandemic. Purposive sampling methodology was used to select a sample of participants which were recruited via Patient Advocacy Groups or patient charities providing support for adrenal insufficiency in the UK (emailing lists and social media). Participants were allocated to their respective groups on a first come-first- serve basis based on their AI type, and country of residence.
Results
Five themes were identified with a total of 18 sub themes. The five main themes were inadequate awareness of AI of the holistic considerations of AI, individuals with AI are experts in their management, lack of access to endocrine specialists to help live well with AI, lack of AI treatment knowledge in health care professionals and limited practical and emotional support. The family carers reported issues with gaining access, lack of appointments over the last 2 years and a lack of knowledge of AI by HCPs, which in some cases resulted in initial misdiagnosis of other conditions such as COVID-19 instead of an AC. A large portion of the feedback received from the focus group interview suggested that the education and training given for the emergency kit was severely lacking. Family carers reported accessing patient advocacy groups (PAGs), extremely helpful in accessing resources for clinical information and as a support mechanism.
Conclusion
The finding will support and guide international standards of care services for families and healthcare professionals, and will inform future research studies in supporting family carers and healthcare services to promote self-care strategies.

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P18

Autonomous cortisol secretion and bone mineral density: Is screening worthwhile?

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Introduction
Some studies have already described an association between mild autonomous cortisol secretion and poorer bone quality and increased risk of fracture. However, no consensus exists on this topic and currently there are no guidelines recommending bone status evaluation in patients suffering from this condition.
Aims
To evaluate bone mineral density in patients diagnosed with autonomous cortisol secretion (ACS) and possible autonomous cortisol secretion (PACS).
Methods
Cross-sectional study with adult patients with ACS or PACS currently under follow-up at our center. The 1mg overnight dexamethasone test was used to define

both entities: PACS if the post-dexamethasone serum cortisol level was 1.9–5.0μg/dL and ACS if it was >5.0μg/dL. Bone mineral density was evaluated by dual-energy x-ray absorptiometry directed at the lumbar spine and femoral neck.
Results
A total of 39 patients were included, 21 (53.8%) of them were women (all post-menopausal). Their median age was 67.0(59.0-73.0) years and their median BMI was 26.6(23.3-29.8) Kg/m^2. 26 (66.7%) were diagnosed with PACS and 13 (33.3%) with ACS. Fourteen (35.9%) patients had type 2 Diabetes mellitus, 16 (41.0%) had dyslipidemia and 8 (20.5%) had obesity. The overall prevalence of osteopenia was 46.2% ($n=18$) and of osteoporosis was 20.5% ($n=8$). When analyzing the prevalence of osteopenia and osteoporosis by subgroups, no significant differences were found between both sexes, in elderly patients, smokers, patients with diabetes or patients with obesity (p>0.05). Patients with bilateral adenomas were not more frequently diagnosed with osteoporosis ($P=0.664$) or osteopenia ($P=0.708$). Similarly, no differences were found in patients that had elevated urinary cortisol ($P=0.515$ and $P=0.124$) or elevated late-night salivary cortisol ($P=0.137$ and $P=0.813$). Patients who had more than one adrenal adenoma were also not more frequently diagnosed with osteoporosis ($P=0.351$) or osteopenia ($P=0.757$), as well as patients with big adenomas –>4cm in diameter – ($P=0.652$ and $P=0.520$). Patients diagnosed with ACS were not more frequently diagnosed with osteopenia than patients diagnosed with PACS (30,8% vs 53,8%, $P=0.173$) but were more frequently diagnosed with osteoporosis (45,5% vs 12,0%, $P=0,026$).
Conclusions
Both osteopenia and osteoporosis were prevalent in patients with PACS or ACS. Comparing to the overall prevalence of osteoporosis in the Portuguese population (10.2%), this numbers were alarmingly high. Therefore, it seems legit to screen for bone disease in this population, in order to provide directed treatment and eventually consider adrenalectomy. It would also be interesting to screen for asymptomatic vertebral fractures and to analyze bone turnover markers in this population.

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P19

RESCUE: Effect of supplemental hydrocortisone during stress in glucocorticoid-induced adrenal insufficiency; A study protocol for a multicentre, randomised, double blinded, placebo-controlled clinical trial

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Background
Long-term, low-dose prednisolone treatment ($\leq$5mg/day) is associated with adrenal insufficiency in >33% of patients. Nevertheless, the clinical consequences of glucocorticoid-induced adrenal insufficiency in patients receiving ongoing low-dose glucocorticoid treatment are unknown. Current clinical guidelines do not recommend routine evaluation of adrenal function during low-dose glucocorticoid treatment, and patients are not routinely instructed to increase glucocorticoid intake during stress.
Aim
To determine the effect of supplemental hydrocortisone during mild to moderate stress on health-related quality of life (HRQoL) in patients with polymyalgia rheumatica/giant cell arteritis (PMR/GCA) receiving ongoing low-dose ($\leq$5mg/day) prednisolone treatment.
Methods
A multicentre, randomised, double blinded, placebo-controlled, clinical trial (EudraCT number 2021-002528-18). The study includes patients with PMR/GCA receiving ongoing prednisolone treatment $\leq$5mg/day. Eligible patients undergo an ACTH test, and 250 patients with a stimulated cortisol $<$420nmol/l (biochemical adrenal insufficiency) are randomised 1:1 to either supplemental doses of placebo or hydrocortisone during stress. Patients continue prednisolone treatment and tapering hereof according to current clinical guidelines and add on supplemental study drug in situations of stress according to the study protocol. In situations of severe stress (risk of developing adrenal crisis), patients receive open label hydrocortisone treatment according to routine clinical care. Seventy-five patients with stimulated cortisol $\geq$420 nmol/l constitute a control group. The participants undergo screening (ACTH test) and baseline examinations, 6 month's HRQoL reporting and follow-up ACTH tests and examinations at 3 and 6 months.
Outcomes
HRQoL is evaluated using a specially developed study smartphone application (app) and with generic and disease-specific questionnaires (SF-36v2, Addiqol-30, CushingQol and Single item Sleep Quality Scale). The app prompts daily 'end-of-day' assessments and obtains information about intercurrent illness, injury, or stress, and symptoms attributable to adrenal insufficiency. The primary outcome is ecological momentary assessments of the Multidimensional Fatigue Inventory, *General Fatigue* scale, in situations of stress. This scale is prompted to the patient five times daily at semi-randomised time points, for three days, if triggered by stress, or at fixed timepoints monthly (unstressed conditions). Secondary outcomes include the other HRQoL measures (key secondary outcomes), incidence and grade of adrenal crises, PMR/GCA treatment characteristics, measures of exogenous Cushing's syndrome (body composition, muscle strength, bone quality, metabolic and cardiovascular risk) and biomarkers for adrenal insufficiency, glucocorticoid sensitivity and action.
Funding
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Status
Recruiting.

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P20

Reduction of albuminuria after surgical and medical treatment of primary aldosteronism

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Introduction
Primary aldosteronism (PA) is a common cause of secondary hypertension that can lead to renal sequelae. Treatment of hyperaldosteronism leads to reductions in albuminuria and glomerular hyperfiltration. We aimed to evaluate the effect of treatment on albuminuria and temporal changes in renal function after treatment with both surgery and medications.
Methods
We prospectively recruited patients with PA over three years. Spot urine samples for albumin were collected at baseline and one-year post-treatment. Degree of albuminuria was categorized based on the KDIGO classification. Serum creatinine values were collected at baseline and annually up to three years post-treatment, while estimated glomerular filtration rates (eGFR) were calculated using the MDRD equation. All patients keen for surgical cure were offered adrenal vein sampling (AVS). Patients with unilateral PA were treated with surgery, while those with bilateral disease were given medical therapy.
Results
Fifty-seven patients were recruited in the study, with no drop-outs. Forty-eight patients underwent AVS, and all had successful bilateral cannulation. Eventually, 25 patients underwent adrenalectomy whilst 32 patients received medications. Patients treated with surgery were younger, had more severe hypokalemia, and were less likely to have ischemic heart disease and hyperlipidemia. Overall, in 18 patients, there was improvement in albuminuria category, it remained the same in 19 patients, and worsened in 5 patients. In the surgical group, albuminuria improved significantly, from median 46.0mg/g to 6.0mg/g, $P=0.001$. In the medical group, albuminuria changed from median 41.5mg/g to 18.5mg/g, $P=0.356$. Significant declines in eGFR after treatment was observed in both groups. In the surgical group, eGFR continued to decline year-on-year until the second year when it stabilized, whereas in the medical group, there was greater eGFR decline in the first year and then it stabilized. Overall, over three years, there was no difference in the magnitude of decline between the surgical and medical groups (8.1ml/min/1.73m^2 vs 7.4ml/min/1.73m^2, $P=0.992$).
Discussion
Treatment of PA leads to reversal of glomerular hyperfiltration and resultant decline in eGFR. However, renal function is subsequently stable after the initial decline. The improvement of renal function is best observed in the improvement

of albuminuria amongst patients with PA, with surgical treatment associated with a greater degree of improvement.

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P21

Transfer Of Congenital Adrenal Hyperplasia Patients From The Pediatric ClinicTo The Adult Clinic: A Single Center Experience

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Introduction

Effective management of the transition from childhood to adulthood in congenital adrenal hyperplasia (CAH) can reduce the problems that may arise in the follow-up during adulthood.

Aim

Evaluation of the clinical characteristics and sociodemographic data of CAH patients transferred from the Pediatric Endocrinology Clinic to the Adult department of our hospital and the comparison of the 2 transition models carried out during this period was the primary aim of this study.

Methods

Thirty-six patients who have been transferred from the pediatric endocrinology clinic to the adult endocrinology clinic between 2001 and 2022 were included in the study. Clinical data were obtained from the hospital medical records. Transition was carried out by two models.While Model 1 included one visit, Model 2 included two visits with an interval of 4-6 months and with participation of pediatric and adult endocrinologists at 'Transition Outpatient Clinic'. Sociodemographic characteristics, frequency and duration of follow-up, clinical features, comorbidities (glucose metabolism disorder, dyslipidemia, TARTs, adrenal crisis,..), treatment modalities, doses and treatment compliance were evaluated and compared according to the transfer model.

Results

Eighteen patients were raised as female and the remaining of them raised as male. Karyotype analysis revealed 46,XX in 47.2% of the patients and 46,XY in 22.2% of them. The mean age $\pm$ SD of cases at transition time was 20.1 $\pm$ 1.8 years (range;17.5-24.2). Consanguineous marriage rate among the parents of the patients was 55.6%. The CAH subtypes were 21 hydroxylase deficiency (61.1%),11 beta hydroxylase deficiency (25%), 17 hydroxylase deficiency (11.1%),and non-classical CAH (2.8%).Of the 36 patients, 19 (52%) were transferred using Model 1 and 17 (47%) using Model 2. There was no difference in terms of comorbidity such as hypertension,glucose metabolism disorder,TARTs,adrenal crisis frequency between the transfer models and also between pediatric and adult follow-up period. Obesity frequency was 22.2% before transition and it was 35.5% after transition.However low bone mineral density was detected in 16.7%($n=4$) patients before and 56.3%($n=9$) patients after transition (p:0.0088). Before transition the percentage of patients receiving hydrocortisone(33.3%) as glucocorticoid option was higher than that in post-transition period (9.7%) (p:0.0018).The hydrocortisone equivalent dose of steroid therapy was also higher before the transition (18.5 $\pm$15.9 mg/m^2/day vs 9.9 $\pm$ 4.7 mg/m^2/day, p:0.002).Pregnancy rate of the cohort was 16.7%.

Conclusion

The two transition models evaluated in our study seem to have no difference in terms of comorbidities and follow-up parameters. It may be more appropriate to compare models in large size cohorts.

Key words

Congenital adrenal hyperplasia, transition, pediatrics

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P22

A Case of Orbital and Adrenal Masses

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Introduction

Adrenal incidentalomas (AIs) are increasingly being identified due to more frequent use of cross-sectional imaging modalities. Recent studies reported AIs being identified in 7.3% of abdominal CT imaging. Most adrenal incidentalomas are adenomas that may have secretory activity.

Case Report

An 80-year-old lady presented to our Emergency department with one week's history of worsening right eye bulging and discomfort. She was found to have right proptosis on examination with no clinical evidence of hormonal excess or deficiency, and her initial blood tests were unremarkable. Her general practitioner arranged for an outpatient CT scan of the chest, abdomen and pelvis that took place earlier that day prompted by the history of anorexia and weight loss of 6kg over two months duration. This CT scan showed a heterogenous solid right adrenal mass measuring 6.9 x 8.1 x 7.8 cm, with numerous enlarged retroperitoneal lymph nodes and nodular thickening of the left adrenal gland. Our Ophthalmology colleagues recommended arranging a MRI orbit, which showed a poorly enhancing right orbit mass measuring 2.4 x 1.7 x 2.0 cm partially encases the optic nerve. Urgent plasma metanephrines and urine steroid profile were sent prior to biopsies, and the treating team was advised to avoid beta blockade pending the results. The patient was found to have a palpable firm right neck lump during her admission and a CT-neck scan confirmed right upper cervical lymphadenopathy. The Ophthalmology team advised that biopsying the orbital mass would be challenging, therefore a right submandibular lymph node biopsy was performed after the plasma metanephrines and urine steroid profile showed normal results. Histology showed a diffuse large B-cell lymphoma of non-germinal centre phenotype. The Haematology team commenced the patient on R-CHOP chemotherapy. The patient was discharged home with follow up with our Haematology and Ophthalmology colleagues. We plan to arrange for abdominal cross-sectional imaging to monitor the response of the adrenal mass to chemotherapy.

Discussion

The adrenal gland involvement in lymphoma is reported in up to 24% of the cases. While benign cortical adenomas are the most common cause for AIs, other differential diagnoses include pheochromocytoma and adrenocortical carcinoma. This case highlights the importance of the prompt multidisciplinary workup and management approach. Careful assessment is required to evaluate for the presence of hormonal deficiency or excess in every case.

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Insulin-like growth factor 2 (IGF2) system role in promoting cell growth in different adrenocortical carcinoma (ACC) cell models

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The majority of adrenocortical carcinomas (ACC) overexpress insulin-like growth factor 2 (IGF2). Although IGF2 drives a proliferative autocrine loop by binding to IGF1R and the isoform A of the insulin receptor (IRA), most studies focused on IGF1R. Recently, a high expression of IRA was observed in ACC vs normal adrenal tissues (NA), suggesting its potential involvement in modulating IGF2 effects in adrenocortical tumorigenesis. Aim of this study was to investigate the specific roles of IGF1R and IR in mediating IGF2 tumorigenic effects in ACC. Western blot analyses showed a higher IGF1R protein expression in both ACC ($n=8$) and adrenocortical adenomas (ACA, $n=8$) vs NA ($n=8$) (mean 1.04 $\pm$ 0.88 and 1.29 $\pm$ 1.11 vs 0.36 $\pm$ 0.12, respectively). Interestingly, although real-time qPCR showed a high variability and no significant differences in IGF1R, IR, IRA and IRB expression among the 3 groups, IRA/IRB ratio was higher than 2 in 5/8 (62.5%) ACC, 1/8 (12.5%) ACA and 0/8 (0%) NA, further supporting an implication of IRA in IGF2 pathway in ACC. Genetic silencing of IGF1R, IR and IGF1R + IR was performed in human ACC cell lines derived from both primary tumor (H295R) and metastasis (MUC-1, TVBF-7) and in 2 primary ACC cultures derived from primary tumor. All cell models used

presented an active IGF2 autocrine loop, as demonstrated by the ELISA assay measuring the presence of IGF2 in culture media. We observed different effects of IGF1R and/or IR knockdown on cell proliferation depending on the cell model. In H295R, neither single nor double IGF1R and IR silencing had an effect on cell proliferation, with no variation on cyclin E1 and B1 expression. Likewise, no changes were detected in ACC primary cultured cells after IGF1R or IR silencing. Instead, in MUC-1 IGF1R knockdown decreased cell proliferation (-19.32 ± 15.48%, $P < 0.01$) and cyclin E1 expression (-30 ± 25%, $P < 0.05$), and a further reduction was observed in IGF1R + IR silenced cells (-47.21 ± 7.18%, $P < 0.001$ vs bas and $P < 0.01$ vs cells silenced for IGF1R) with a diminished expression of both cyclin E1 (-36 ± 26%, $P < 0.05$) and cyclin B1 (-55 ± 37%, $P < 0.01$). Similarly, in TVBF-7, even if no variations were found after IGF1R or IR silencing, a significant reduction was observed in IGF1R + IR silenced cells (-44.08 ± 10.52%, $P < 0.001$). In conclusion, our preliminary data showed a high heterogeneity among different cell models with a tumor-specific role of IGF1R and IR, and seem to suggest that these receptors play a key role in promoting cell growth in ACC metastases but not in primary tumor.

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Whole Exome Sequencing Identified Mutations in Genes Involved in the Synthesis of Atrial Natriuretic Peptide from the Heart in Hypertensive Cardiovascular Disease Patients

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The heart not only has a mechanical function of pumping blood through vessels but also acts as an endocrine gland. In its endocrine function, the heart releases atrial natriuretic peptide (ANP), a hormone of a large family of natriuretic peptides. ANP is secreted from cardiac atria as an inactive preprohormone. In post-translational modification, 25-amino acid signal sequence is cleaved from preprohormone to produce proANP of 126-amino acid, which is the major form of ANP stored in intracellular granules of atria. Following stimulation of atrial cells by increased blood pressure, proANP is released and rapidly converted to 28-amino acid C-terminal mature ANP on cell surface by cardiac transmembrane serine protease corin. ANP regulates salt-water balance and blood pressure by promoting renal sodium and water excretion and stimulating vasodilation. Among other factors, calcium dependent secretion activator (CADPS) is one of the proteins that controls ANP secretion from the heart in stressed situations. Defects in the ANP pathway contribute to major diseases such as hypertension, cardiac hypertrophy and heart failure. The present study was designed to screen hypertensive cardiovascular patients to determine possible pathogenic mutations in genes involved in the synthesis of ANP from the heart using whole exome sequencing (WES). Thirteen hypertensive cardiovascular patients from three families (3 patients in 1st, 21-48 years; 5 in 2nd, 43-72 years and 5 patients in 3rd, 19-47 years of age) were selected for WES. DNA Isolation Kit (QIAamp DNA mini-Kit) was used to extract genomic DNA at City Lab, Rawalpindi, Pakistan, which was then taken to Genome Institute of Singapore (GIS), Singapore, where final dilutions of 25µl DNA were outsourced to Proteomics Lab, Macrogen Asia Pacific, Singapore for WES. Subsequent bioinformatics analysis was performed at GIS, Singapore. We identified 3 mutations in 2 genes, *CADPS* and *CORIN*, involved in the synthesis of ANP from the heart. Two variants in *CADPS* gene were observed; one splicing likely pathogenic variant (c. 969 + 3A>G) in all patients of family 1 and other missense (c. 308A>C, p. Glu103Ala) variant of uncertain significance (VUS) was witnessed in two patients of family 2. Both variants were already reported but are extremely rare in GnomAD database. In addition, a novel splicing (c. 618-2_618-1insT) VUS was identified in *CORIN* gene in only one patient of family 1. In conclusion, our results identified mutations in two genes involved in the synthesis of ANP from the heart, which may cause hypertension related cardiovascular diseases.

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Pregnancy outcomes in women with classic and non-classic congenital adrenal hyperplasia

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Background
There have been conflicting reports on fertility, reproduction rates and pregnancy outcomes in women with congenital adrenal hyperplasia (CAH). Identification of potential modifiable influential factors of pregnancy outcomes in these women has been hampered in the past by either small sample sizes or data derived from epidemiological samples.
Methods
Retrospective multi-center study including a total number of 72 women with CAH ($n = 34$ Non-classic (NC), $n = 21$ simply virilizing (SV), $n = 17$ with salt wasting (SW).) Data on pregnancies were collected using self-designed questionnaires, patients' and maternity records. In total, 133 pregnancies, 112 live births and 25 abortions were documented.
Results
Median age of the first pregnancy was 30.0 years and did not significantly differ between phenotypes. Across the entire cohort, it took almost two years on average to become pregnant for the first time (median 18.0 months, n.s.). Of all women 83.9% became pregnant spontaneously while the remaining had to use assisted reproductive techniques. The average number of life births of 1.4-1.6 children per woman was similar between all three groups ($P = 0.813$) and comparable to the general population. There was also no significant group difference in terms of spontaneous abortions (0.2-0.6 per women, $P = 0.360$). Most of the children in our cohort were delivered in a timely manner, however, rates of primary cesarean section in all groups were higher than those reported for the general population (NC 45.2%, SV 76.2%, SW 70,6%; $P = 0.056$). Of all children 11.3% in our cohort were small for gestational age (SGA), without a difference between phenotype groups. Gemini pregnancies were documented in 7 cases, 4 of whom had undergone assisted reproduction. Pregnancy complications such as gestational diabetes ($n = 3$) and pre-eclampsia ($n = 2$) were rare. Of the 42 women who had a cesarean section at the birth of their first child, ten were unplanned, including four cases required emergency cesarean section.
Conclusion
Our findings indicate that latency to first pregnancy is still prolonged in patients with CAH independent of phenotype, while fertility rates are comparable to the general population. Rate of primary cesarean sections were not only high in women with classic but also with non-classic CAH.

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Response to Crinecerfont Treatment in Adults with Classic Congenital Adrenal Hyperplasia Is Correlated with Elevated Baseline Hormone Levels But Not Glucocorticoid Dose

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Introduction
Corticotropin-releasing factor type 1 (CRF_1) receptor antagonists, such as crinecerfont, have recently been investigated for the treatment of classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD), a rare autosomal disease characterized by cortisol deficiency, elevated adrenocorticotropic hormone (ACTH), and excess androgen production. In a study of adults with 21OHD, treatment with crinecerfont for 14 days led to median percent reductions of >60% for 17 hydroxyprogesterone (17OHP, -64%), ACTH (-66%), and androstenedione (-64%) . Post hoc analyses were conducted to assess whether baseline hormone levels and glucocorticoid (GC) dose correlated with treatment response.
Methods
Males and females (18-50 years) with 21OHD and elevated 17OHP concentrations (≥1000 ng/dL) were studied in a sequential cohort design with the following open-

label crinecerfont regimens: 50 or 100 mg once daily at bedtime (cohorts 1 and 2, respectively); 100 mg once daily with the evening meal (cohort 3); 100 mg twice daily with meals (cohort 4) for 14 days. Participants could enroll in more than 1 cohort. Correlations between baseline ACTH, 17OHP, androstenedione, GC dose, and magnitude of change from baseline (CFB) to Day 14 hormone levels were assessed using the average concentration of samples collected before the morning GC dose (0600h, 0800h, and 1000h) as well as the average concentration over a full 24-hour sampling period.
Results
Eighteen participants (11 women, 7 men) were enrolled: cohort 1 ($n=8$), cohort 2 ($n=7$), cohort 3 ($n=8$), cohort 4 ($n=8$). Baseline GC regimens included hydrocortisone ($n=10$), prednisone or equivalent ($n=7$), and hydrocortisone + prednisone or equivalent ($n=1$), with mean total daily dose (hydrocortisone equivalent) of 14 mg/m^2/day (range, 6-25). Significant correlation was found between baseline concentration and CFB to Day 14 for 17OHP (morning window, $r=0.735$; 24 hour average, $r=-0.646$), with the greatest reductions from baseline observed in participants with the highest baseline concentrations. Similar correlations were observed for ACTH (morning window, $r=0.906$; 24-hour average, $r=-0.828$) and androstenedione (morning window, $r=0.887$; 24-hour average, $r=-0.898$). No correlation was found between baseline GC dose and CFB to Day 14 for 17OHP (morning window, $r=0.115$; 24-hour average, $r=0.215$).
Conclusions
In adults with 21OHD treated with crinecerfont, there was a high correlation between androgen and precursor treatment response and baseline hormone levels, but not with baseline GC dose, indicating that those with more elevated baseline hormone levels could have greater response, whereas androgen reduction could occur across a broad range of GC doses.

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Can Inflammation-Based Scores Help Predict Treatment Response in Advanced Adrenocortical Carcinoma?

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Background
Treatment for advanced adrenocortical carcinoma (ACC) consists of mitotane alone or combined with etoposide, doxorubicin and cisplatin (EDP), yet their efficacy is limited and burdened with significant toxicity. Moreover, markers of response are lacking. Inflammation-based scores have been proposed as prognostic factors in several malignancies including ACC, and recently also as predictors of gemcitabine + capecitabine efficacy, second-line treatment in progressive disease. We therefore investigated the role of inflammation-based scores in predicting response to first-line therapy in advanced ACC.
Methods
We performed a retrospective analysis of patients with advanced ACC treated with mitotane alone or EDP ± mitotane in two European centres. We investigated clinical parameters (tumour stage at diagnosis, resection status, Ki67 index, time from diagnosis to treatment start, performance status, plasma mitotane levels, time in mitotane target ≥80%, cortisol hypersecretion at treatment initiation) and pre-treatment inflammation-based scores [neutrophil-to-lymphocyte-ratio (NLR), platelet-to-lymphocyte-ratio (PLR), monocyte-to-lymphocyte-ratio (MLR), derived neutrophil-to-lymphocyte ratio (dNLR), serum albumin]. Primary and secondary endpoints were overall-survival (OS) and time-to-progression (TTP) from treatment initiation, respectively. We additionally evaluated the best objective response to treatment, defined according to RECIST 1.1 criteria.
Results
We included 90 eligible patients (59% women, median age: 51 years) treated with mitotane monotherapy ($n=40$) or EDP ± mitotane ($n=50$). In the mitotane cohort, NLR ≥ 5 and PLR ≥ 190 predicted shorter OS (HR: 145.83, 95%CI: 1.87-11323.83, $P=0.025$; HR: 165.50, 95%CI: 1.76-15538.04, $P=0.0027$, respectively), remaining significant at Cox regression multivariable analysis including resection status, time from diagnosis to start treatment, ECOG performance status, cortisol hypersecretion and time in mitotane target. NLR was also associated with shorter TTP (HR: 2.58, 95%CI: 1.28-5.20, $P=0.008$), but only at univariable analysis. Patients with NLR ≥ 5 showed a worse response to mitotane than those with NLR < 5 ($P=0.040$). In the EDP cohort, NLR ≥ 5 predicted shorter OS (HR: 2.52, 95%CI: 1.30-4.88, $P=0.006$) and TTP (HR: 1.95, 95%CI: 1.04-3.66, $P=0.037$), which was not confirmed at multivariable analysis.
Conclusion
Inflammation-based scores, calculated from routinely measured parameters, may help predict response to first-line pharmacotherapy in advanced ACC. These findings will be validated in larger cohorts.

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The impact of Bariatric Surgery on the 1mg Dexamethasone Suppression Test in patients with Severe Obesity

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Background
The cortisol suppression test with 1 mg dexamethasone (DST) is a screening test for hypercortisolism with high sensitivity (95%) for serum cortisol cut-off < 1.8 µg/dl. However, cortisol tests may give false positive in patients with severe obesity (SO). On the other hand, bariatric surgery (BS) is the most effective treatment for SO, and the operated population is growing. At present there is no reliable data regarding the impact of BS on DST results in patients with SO, as well as on the role of the DST as predictor of response to BS. On these bases we performed the present study.
Objectives
a) To explore the impact of BS on the results of the DST. b) To evaluate the impact of cortisol suppression on the response to BS (in terms of weight loss).
Methods
Prospective study including patients with SO scheduled for BS at our site between January-2019 and March-2020. Patients with overt clinical endogenous hypercortisolism or corticosteroid treatment were excluded. All the patients underwent at baseline and 12 months after BS complete medical history, anthropometric data, biochemical analysis and DST.
Results
23 patients were included, 69.6% females, mean age 44.4 ± 9.3years, BMI 45.97 ± 8.23kg/m^2, excess weight (EW) 59.76 ± 25.07 kg (according to BMI 25kg/m^2). All the patients presented DST < 1.8ug/dl before BS, while 1 case had a higher cortisol value after BS. Cortisol after DST was significantly higher 12m post-BS than baseline (0.82 ± 0.29ug/dl vs 0.94 ± 0,31 ug/dl, $P=0.05$). There was direct correlation between BMI and DST suppression level at baseline ($P<0.01$), without any relationship with age, gender, menopausal state or associated comorbidities. Regarding weight response to BS, 11 (47.8%) patients achieved a weight loss of >75% of the EW at 12m. Patients with a suppression of cortisol < 0.8 ug/dl were less likely to achieve this threshold ($P<0.02$, AUC 0.79, S 0.73 and E 0,75) ($P=0.03$)
Conclusions
All the patients with SO suppressed cortisol below 1.8 ug/dl in the pre-BS DST. Cortisol after DST increases following BS, and may not suppress properly in some patients. A DST cortisol threshold < 0,8 ug/dl before BS predicted a lower weight loss, reaching less than 75% of the EW at 1 year.

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Role of macrophages in zona glomerulosa differentiation

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Maturation of the definitive adrenal cortex occurs between 3 and 6 weeks post-partum and involves onset of CYP11B2 expression and establishment of the laminin-encased 3D structure of glomeruli that contain rosettes of 10 to 15 zona

glomerulosa (zG) cells that work in coordination to produce optimal amounts of aldosterone. Although this process is dependent on canonical WNT/b-catenin signaling, cellular sources of WNT ligands remain elusive and the mechanisms involved in the extensive extra-cellular matrix remodeling associated with rosette/glomeruli morphogenesis are unknown. Beyond their role in innate immunity, macrophages are involved in extra-cellular matrix remodeling under a wide variety of pathophysiological conditions and have the capacity to produce WNT ligands. This, together with the presence of macrophages within the zG cells, strongly suggest that macrophages may play a role in zG morphogenesis and differentiation. Supporting this idea, a recent publication has shown that intra-tissular aldosterone concentration was reduced in the absence of macrophages under stress conditions. However, whether macrophages play a direct role in controlling aldosterone secretion or an indirect role by remodelling the postnatal zG is unknown. The presence of tissue resident macrophages in a specific zone is dependent on the production of trophic factors such as IL34, CSF1, CSF2 or CX3CL1 by nearby, tissue resident 'niche' cells. In return, macrophages are thought to provide positive 'feedback' signals to their niche, generating mutually beneficial circuits between the niche and its macrophages. To gain insight into the role of macrophages in zG morphogenesis and homeostasis, we used single cell sequencing and RNAscope analyses to show expression of CX3CL1 in the zG and of CX3CR1 in macrophages. Interestingly, CX3CL1 expression in the zG was downstream of WNT signalling, suggesting existence of a bi-directional interaction between macrophages and zG. To further study the role of macrophages during the maturation of the zG, we pharmacologically depleted macrophages by the small molecule inhibitor Pexidartinib at different time points between 3- and 12-weeks post-partum, when maturation of the zG occurs. Short-term depletion of macrophages resulted in a more disorganized and elongated zG, suggesting a delay in maturation. However, long-term depletion of macrophages resulted in exacerbated maturation of the rosettes, suggesting that the short-term zG defect was followed by establishment of a compensatory mechanism to allow formation of rosettes even in the absence of macrophages. Whether these perturbations of the zG are correlated with an altered production of aldosterone is still under study.

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Bone metabolism and dual-release Hydrocortisone: results from a real-life study

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Background
Patients with adrenal insufficiency (AI) require long-term glucocorticoid (GC) replacement therapy and generally show an increased prevalence of bone metabolism alterations. Only few data are available on bone safety of dual-release Hydrocortisone (DR-HC) therapy.
Objective
To evaluate bone metabolism in both primary AI (PAI) and secondary AI (SAI) during long-term therapy with DR-HC.
Methods
We studied patients with AI on short-acting, immediate-release GC therapy (hydrocortisone or cortisone acetate) before and up to 60 months after the switch to an equivalent dose of DR-HC, collecting data on bone turnover markers, femoral and lumbar spine areal bone mineral density (aBMD) and trabecular bone score (TBS). Any concomitant condition (hypo- or hyperparathyroidism, early menopause, malignancies) or medication (PTH, anti-resorptive therapy) that could influence bone parameters was considered as exclusionary.
Results
31 patients (18 PAI and 13 SAI, 18 females, 9 post-menopausal) with a median age of 51 (range 20-77) years, were included. Patients on established immediate-release glucocorticoid therapy were switched to an equivalent dose of DR-HC at baseline. Median duration of AI at baseline was 36 months (range 12-432). Median daily hydrocortisone- equivalent doses before switching to DR-HC were 14.7 [12.0-17.3] mg/kg/m2 in PAI and 11.0 [10.1 – 13.2] mg/kg/m2 in SAI. Any other hormonal disorders (i.e. diabetes, hypothyroidism, hypogonadism, Growth Hormone deficiency) were adequately controlled throughout the study. All patients had normal calcium and phosphorus levels and most were under cholecalciferol therapy, with mean Vit D 30.0 $\pm$13.2 ng/mL at baseline. At baseline, 48% of patients had aBMD values compatible with osteopenia and 16% had a diagnosis of osteoporosis in at least one site. Compared to baseline, no significant difference was observed in aBMD at femur neck, total hip and total lumbar spine at 24 (P= .825; P=.453; P=.637), 36 (P=.637; P=.460; P=.607), 48 (P=.202; P=.996; P=.379) and 60 months (P=.175; P=.528; P=.983) of DR-HC therapy. Interestingly, TBS values significantly decreased after 48 (P=.021) and 60 months (P=.032), although a physiological decline of bone microarchitecture with aging is expected. Alkaline phosphatase, C-terminal telopeptide and osteocalcin levels showed no differences in all timepoints. Moreover, no differences were found between PAI and SAI patients in all the evaluated parameters.
Conclusions
DR-HC is a safe treatment option in terms of bone health in patients with AI, maintaining stable bone mass, bone quality and bone turnover while aging.

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Inflammation-based scores in benign adrenocortical tumours are related to the degree of cortisol excess

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Glucocorticoids play a significant role in immune modulation and regulation of inflammation. In patients with endogenous glucocorticoid excess (Cushing's syndrome [CS]) multiple haematological alterations are recognized, such as neutrophil leukocytosis, lymphopenia, and eosinopenia, often leading to severe clinical complications. However, little is known in patients with mild autonomous cortisol secretion (MACS). Serum inflammation-based scores may reliably reflect systemic inflammation and predict outcomes in several diseases. The aim of this study was to evaluate inflammation-based scores in patients with ACTH-independent cortisol excess and investigate their relationship with cortisol hypersecretion levels. A cohort of 391 patients (median age 61 years, 59.6% women) was evaluated: 231 patients with nonfunctioning adrenocortical tumors (NFAT), 138 with MACS (serum cortisol after 1-mg overnight dexamethasone suppression test >50 nmol/l and absence of typical CS features), and 22 with CS. Patients with other types of benign adrenal tumours (e.g. myelolipoma), phaeochromocytoma, active malignancies, infections, and autoimmune or haematological diseases were excluded. We evaluated the cortisol profile and the following inflammation-based scores at initial diagnosis: Neutrophil-to-Lymphocyte Ratio (NLR), Lymphocyte-to-Monocyte Ratio (LMR), Platelet-to-Lymphocyte Ratio (PLR), Systemic Immune-Inflammation Index (SII, obtained by multiplying absolute platelet count and NLR), and Prognostic Nutrition Index (PNI, calculated by serum albumin and lymphocyte count reflecting immune-related nutritional status). Data are expressed as median (interquartile range). Serum cortisol after 1-mg overnight dexamethasone positively correlated with NLR (r=0.283) and SII (r=0.225) and negatively with LMR (r=-0.23) (each $P<0.001$). NLR, SII and LMR significantly differed among the three groups of patients, while PLR and PNI were similar among CS, MACS and NFAT. In particular, NLR and SII were significantly higher in both CS [3.80(1.92-4.37) and 859.6(459.7-1355.2)] and MACS [2.71(2.05-3.60) and 730(485.9-961.5)] compared to NFAT [2.21(1.68-2.94) and 562.9(412.1-837.6)] (P=0.001 and $P<0.001$ for NLR and P=0.002 and P=0.01 for SII, respectively). On the contrary, LMR was lower in patients with CS [2.23(1.82-3.47)] and MACS [3.12(2.42-4.5)] than in those with NFAT [3.62(2.85-4.55)], but also significantly lower in CS compared to MACS, all $P<0.05$. In conclusion, the neutrophil-based scores (NLR and SII) and monocyte-based score (LMR) correlated with the degree of endogenous cortisol excess being altered in both patients with ACTH-independent CS and MACS. Moreover, LMR was the only score that showed a significant difference between CS and MACS. These findings suggest that, similar to overt CS, mild autonomous cortisol excess also influences the immune system function which can contribute to the MACS-associated comorbidities.

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Primary hyperparathyroidism and bilateral pheochromocytoma with MAX mutation: Case report

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Introduction
Pheochromocytomas(PC)are rare catecholamine-producing neuroendocrine tumors. Germline variants of the MYC-associated factor (MAX) gene have been associated with familial PC and paragangliomas (PGL) with an autosomal dominant pattern of inheritance and an overall frequency estimated at 1.9%. Other endocrine and non endocrine tumors can be associated to germline MAX mutations.
Case presentation
We report a case of a 37 years old male patient, with no particular personal or family history, who presented with a bilateral PC diagnosed following severe hypertension with paroxysmal Menard's triad, high urinary normetanephrine = 32.26 µmol/24h (> 10x normal value, confirmed the diagnosis of PC). Abdominal CT scan showed 3 bilateral adrenal nodules. MIBG scintigraphy showed no suprarenal or extra suprarenal fixation. Patient underwent a bilateral adrenalectomy and histologic study confirmed the diagnosis of PC(PASS <3). A truncating heterozygous germline MAX variant located on exon 4(c.223 C>T(p.Arg75*)was identified. Reassessment at 3 years after surgery showed no signs of recurrence (no hypertension and negative urinary metanephrins) .Moreover, our patient's lab findings were compatible with an asymptomatic hypercalcemic primary hyperparathyroidism(PHPT), a superior parathyroid nodule was found on cervical ultrasound with a significant in-situ PTH level (5059pg/ml). Patient was referred to surgery for parathyroidectomy.
Discussion
The MAX gene is the tenth PCC/PGL susceptibility gene described, it encodes a transcription factor involved in cell proliferation, differentiation and apoptosis. this mutation is responsible for multiple and/or bilateral PCs and PGL. The biological pattern of catecholamine secretion with a predominance of normetanephrines described in this mutation and explained by a low expression of the PNMT enzyme was found in our patient. Hypercalcemia has been reported in 4 other individuals with germline MAX mutations and PC, one of them reported as PHPT with germline MAX pathologic variant(PV):c.223C >T(p.Arg75*)which is similar to the variant of our patient suggesting that this variant may be associated with PHPT with parathyroid adenoma. Other endocrine and non-endocrine tumors that have been occasionally reported in this syndrome are absent in our patient.
Conclusion
Germline MAX mutations are associated with PCs, PGLs, parathyroid adenomas, other endocrine and non endocrine tumors suggesting that MAX is a novel multiple endocrine neoplasia gene. Screening of PHPT should be considered in the individuals carrying the PV c.223C>T (p.Arg75*).First-degree relatives of an individual with a known *MAX* pathogen variant should be offered molecular genetic testing.

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P281

The cardiometabolic risk in patients with non-functioning adrenal incidentaloma: an observational, retrospective and propensity score matched study

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Introduction
Recent studies found an increased cardiometabolic risk in patients with Non-Functioning Adrenal Incidentaloma (NFAI), but all these data have low quality of evidence.
Objective
To establish whether cardiometabolic risk and complications in NFAI patients can be associated to the presence of a non-secreting adrenal tumor, independently from potential confounding factors.
Subjects and Methods
In this cross-sectional and retrospective study, all the NFAI patients referred to the University Hospital of Turin, between 2000 and 2022, were consecutively enrolled and compared with subjects not affected by adrenal disease. For each patient, clinical and biochemical data were evaluated, in addition to their cardiovascular (CV) risk scores and cardiometabolic outcomes.
Results
A total of 2381 subjects were enrolled in the study (1137 patients with NFAI, including 831 with arterial hypertension and 306 with normal blood pressure values; 1244 non-NFAI, of which 1177 hypertensive patients and 67 normotensives). In the NFAI group, a significant increase of the CV risk was observed exclusively among subjects suffering from hypertension and it was calculated using risk scores (SCORE: $4.93 \pm 5.79\%$ vs $3.94 \pm 6.77\%$, $P=0.006$; Framingham Risk Score: $11.03 \pm 9.32\%$ vs $9.45 \pm 8.97\%$, $P=0.002$; Cuore project: $15.63 \pm 15.66\%$ vs $11.46 \pm 13.42\%$, $P=0.000$). Moreover, the NFAI group presented globally higher AASI (Ambulatory Arterial Stiffness Index) values compared to the subjects with no adrenal mass, both among patients with arterial hypertension (0.47 ± 0.16 vs 0.43 ± 0.14; $P=0.022$) and among those with normal blood pressure values (0.45 ± 0.14 vs 0.31 ± 0.08; $P=0.012$). Regarding cardiometabolic complications, at multivariate logistic regression, NFAI proved to be independently associated with aortic ectasia (OR 2.779, 95% CI 1.287-6.001, $P=0.009$), correcting for age, sex, metabolic syndrome (MS) and previous CV events. To minimize the impact of differences between the NFAI and non-NFAI groups, propensity score matching (1:1) was used. Even in this analysis, NFAI retained a statistically significant association with aortic ectasia ($\beta=0.074$, 95% CI 0.016-0.131, $P=0.012$). The matching variables were the same covariates applied in the logistic regression. Conversely, no significant associations with MS, type II diabetes, eGFR <60 mL/min/1.73m^2, microalbuminuria, atrial fibrillation or hypertensive cardiomyopathy were found.
Conclusions
The results of this study suggest the presence of an augmented cardiometabolic risk in patients affected by NFAI. Considering cardiometabolic complications, we described for the first time an association between NFAI and aortic ectasia. If these data will be confirmed in longitudinal studies, NFAI could be considered a condition of high cardiovascular risk and, therefore, patients with this disease could benefit from appropriate cardiometabolic follow-up and treatment.

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P282

Characterisation of a Three-Dimensional (3D) Cell Culture Model of Adrenocortical Carcinoma

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Adrenocortical carcinoma (ACC) is a rare malignancy associated with a poor prognosis (1). Current treatments are limited with surgical resection the only option for a complete cure (2). The development of translational therapies is limited by pre-clinical disease models. Three-dimensional (3D) cell culture models can accurately reflect the tumour micro-environment but are lacking in ACC (3). In the current study, we developed and characterised novel 3D models of MUC-1, HAC15 and H295R within a type-1 Collagen matrix. Viability of each model was assessed by Sytox Blue staining. Live/dead imaging using confocal microscopy was carried out to determine the distribution of live and dead cells within the 3D models. Metabolic activity was assessed via AlamarBlue staining with Ki67 detecting proliferation. Steroidogenic capacity was determined using Liquid chromatography tandem mass spectrometry and real time- polymerase chain reaction (RT-qPCR). The morphology of the cells was imaged using confocal microscopy. All cells were successfully cultured in a type 1 collagen matrix. H295R and MUC-1 models show optimum viability up until day 7 but a decrease compared to when the corresponding cell line was cultured in monolayer. HAC15 model maintains a constant level of viability over 21 days in culture. All three models increase their metabolic and proliferative activity over time. All were steroidogenic, with HAC15 and H295R cells showing an increased expression of aldosterone when stimulated with angiotensin II when cultured in 3D compared to monolayer. Decreased levels of cortisol production were reported in all 3D models compared to when cultured in monolayer. In the current study, we successfully developed 3D cell culture models for ACC. Each cell line in a 3D model showed behaviour reflective of the 3D tumour micro-environment. Each cell line in a 3D model showed: (i) lower overall viability compared to monolayer- reflective of cell turnover and necrosis in the 3D tumour microenvironment, and (ii) an increase in metabolic

activity and proliferation reflective of cell turnover in the 3D microenvironment. Similar findings have been shown in the literature for other 3D cancer cell culture models. All were steroidogenic in nature. This model will be used in the future studies to test novel and traditional therapeutics to test the translational relevance of this model to ACC, as a reliable, animal sparing model.

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P283

Comparison of Plasma Levels of Metanephrines Obtained by Direct Venipuncture vs Indwelling Intravenous Cannula in Hypertensive Patients

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Background
The diagnosis of pheochromocytoma and paraganglioma (PPGL) requires the measurement of plasma metanephrines; however, several pre-analytical parameters can lead to false positive test results. During venipuncture, pain perception may activate the sympathetic nervous system, increasing catecholamine metabolite levels. Furthermore, hypertension patients exhibit sympathetic hyperactivity compared to normotensive subjects. The purpose of this study was to compare the plasma levels of metanephrines obtained by direct venipuncture to those obtained by an indwelling intravenous cannula in hypertensive patients, as well as the effect of pain intensity on plasma levels of metanephrines.
Methods
Sixty-eight hypertensive patients, 17 men and 51 women, with a mean age of 55 years (range 31-77 years) were enrolled in the study. After at least 30 minutes of supine rest, we collected blood samples through an indwelling intravenous cannula and then promptly via direct venipuncture on the contralateral arm. A visual analogue scale was used to gauge the level of pain experienced during blood collection. Plasma concentrations of free metanephrines, which included plasma free metanephrine, normetanephrine, and 3-methoxytyramine, were determined by the liquid chromatography-tandem mass spectrometry method.
Results
Plasma normetanephrine levels obtained by direct venipuncture were significantly higher than those obtained by an indwelling intravenous cannula (mean difference 4.14 pg/mL; 95% CI 0.22 to 8.06; p-value 0.039 and mean percentage difference 8.06%; 95% CI 2.44 to 13.69%; p-value 0.006). However, the sample results were within the reference range. On the contrary, plasma levels of 3-methoxytyramine and metanephrine did not differ substantially between the two sampling techniques (mean difference 1.26 ng/L, 95%CI -0.44 to 2.95 and -0.98 pg/mL; 95%CI -2.52 to 0.56, respectively). Furthermore, there was no correlation between pain score and variation in plasma metanephrine levels.
Conclusions
This study proposes an optimal sample collection route using an indwelling intravenous cannula for the diagnosis of PPGL among hypertensive patients. Despite the minimal differences, clinicians should be aware that this pre-analytical component could cause incorrect diagnoses and unnecessary investigations.

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P284

Prevalence of autonomous cortisol secretion in patients with primary aldosteronism and its implications on the cardiometabolic profile and on surgical outcomes

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Purpose
To evaluate the prevalence of autonomous cortisol secretion (ACS) in patients with primary aldosteronism (PA) and its implications on cardiometabolic and surgical outcomes.
Methods
A retrospective multicenter study of PA patients who underwent 1mg-dexamethasone suppression test (DST) in follow-up in 21 Spanish tertiary hospitals. ACS was defined as a cortisol post-DST >1.8μg/dL (confirmed ACS if >5μg/dL and possible ACS if between 1.8-5μg/dL) in absence of specific clinical features of hypercortisolism. A control group with ACS without PA (ACS group) matched by age and DST levels was included for comparing the cardiometabolic profile with the ACS-PA group.
Results
The prevalence of ACS-PA in the global cohort of patients with PA ($n=176$) was 29.0% ($n=51$). Ten patients had confirmed ACS and 41 possible ACS. The cardiometabolic profile of patients with ACS-PA and PA was similar, except for an older age (59.3 ± 11.22 vs. 55.5 ± 11.87 years, $P=0.049$) and a larger tumor size of the adrenal lesion (24.4 ± 14.01 vs. 17.3 ± 6.84mm, $P<0.001$) in the ACS-PA group. Additionally, as it would be expected, cortisol post-DST were higher (4.1 ± 4.20 vs. 1.1 ± 0.40μg/dL, $P<0.001$) and ACTH levels lower (15.0 ± 10.97 vs. 20.2 ± 10.55 pg/mL, $P=0.030$) in ACS-PA patients than in the PA group. When comparing the ACS-PA group ($n=51$) and the ACS group ($n=78$), the prevalence of hypertension (OR 7.7 [2.64-22.32]) and of cardiovascular events (OR 5.0 [2.29-11.07]) was higher in ACS-PA patients than in ACS patients. However, patients with isolated ACS presented greater levels of HbA1c than ACS-PA patients (5.8 ± 0.82 vs. 6.5 ± 1.47%, $P=0.024$). Of the 176 patients of the PA cohort, 59 underwent adrenalectomy: 20 of the ACS-PA group and 39 of the PA group. Biochemical cure was reached in 94.9%, hypertension cure in 37.3% and hypertension improvement in 54.3%. The coexistence of ACS in patients with PA (ACS-PA) did not affect the surgical outcomes, being the proportion of biochemical and clinical cure similar between ACS-PA and PA groups (100% vs. 92.3%, $P=0.203$ and 45.0% vs. 33.3%, $P=0.380$, respectively). When compared patients with ACS-PA who underwent adrenalectomy ($n=20$) and those medically treated ($n=31$), no differences in the evolution of the cardiometabolic profile was detected between both groups, but surgery led to a greater increase in serum potassium levels.
Conclusion
Co-secretion of cortisol and aldosterone affects a third part of patients with PA. Its presence is more common in patients with larger tumors and an older age. However, the cardiometabolic and surgical outcomes of patients with ACS-PA and PA are similar.

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P285

Predictive performance of aldosterone-to-renin ratio in the diagnosis of primary aldosteronism in patients with resistant hypertension

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Background
The systematic use of confirmatory tests in the diagnosis of primary aldosteronism (PA) increases costs, risks and complexity to the diagnostic work-up. In light of this, some authors proposed aldosterone-to-renin (ARR) cut-offs and/or integrated flow-charts to avoid this step. Patients with resistant hypertension (RH), however, are characterized by a dysregulated renin-angiotensin-aldosterone system, even in the absence of PA. Thus, it is unclear whether those strategies might be applied with the same diagnostic reliability in the setting of RH. Aim of this study was to evaluate the predictive performance of the ARR in the diagnosis of PA in a prospective cohort of patients with true RH. More specifically, we set out to determine whether specific ARR cut-offs could allow the unambiguous identification of patients with PA, without the need of a confirmatory test.
Methods
We prospectively enrolled 129 consecutive patients diagnosed with true resistant hypertension and no other causes of secondary hypertension. All patients underwent full biochemical assessment for PA, including both basal measurements and saline infusion test (SIT). PA was diagnosed when the following conditions were met at the same time: baseline plasma aldosterone concentration (PAC) $\geq$ 15 ng/dL, ARR $\geq$ 40 (ng/dL)/(ng/mL/h), and PAC after SIT $\geq$ 10 ng/dL.
Results
34/129 patients (26.4%) were diagnosed with PA. Among basal measurements, the parameter that provided the best diagnostic performance was ARR, which displayed a moderate accuracy in distinguishing patients with PA from those with essential RH (AUC = 0.883). At multivariable logistic regression, serum potassium levels were identified as the second-best predictor of PA. After stratifying the patients according to the presence/absence of hypokalemia, an ARR > 238.4 (ng/dL)/(ng/mL/h) provided a 100% specificity for the diagnosis of PA in normokalemic patients, with a sensitivity of 25% (AUC = 0.852). An ARR > 115.6 (ng/dL)/(ng/mL/h) provided a 100% specificity for the diagnosis of PA in hypokalemic patients, with a sensitivity of 64% (AUC = 0.941).
Conclusions
Among normokalemic patients, there is a wide overlap in ARR values between those with PA and those with essential RH; the possibility to skip a confirmatory test should thus be considered with caution in this setting. A better discriminating ability can be seen in the presence of hypokalemia; in this case, ARR alone may be sufficient to skip confirmatory tests in a suitable percentage of patients.

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Regulation of stem/progenitor cells of the HPA axis during stress adaptation

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Chronic stress is a pervasive concern in the modern society. A long-term hyper activation of the hypothalamic-pituitary-adrenal (HPA) axis leads to elevated amounts of stress hormones [e.g. ACTH and glucocorticoids (GCs)]. This can incur maladaptation that eventually contributes to mental illness, cardiovascular dysfunctions, diabetes, cancer and autoimmune diseases. Emerging key players for stress adaptation of the HPA axis are stem/progenitor cell populations. In this study, we aim to unravel the mechanisms involved in the regulation of stem/progenitor cells of the HPA axis during stress adaptation. To that aim, we incorporated an *in vitro* system of non-adherent spheroids from primary adrenocortical mouse cells that were stimulated with ACTH. The treatment resulted in the increased growth of the spheroids compared to unstimulated controls indicating a potential role of the hormone in cell proliferation and stem cell behaviour. This result is in line with the enlarged adrenals observed in patients with Cushing's syndrome. To assess the contribution of stem cells during stress adaptation in the adrenal cortex *in vivo*, we performed immobilization stress and lineage tracing studies using the tamoxifen inducible *Gli1:CreERT2/R26R:eYFP* mouse line. By combining these results along with single-cell RNA-seq technology, we aim to shed light into molecular factors involved in the adult adrenal cortex regeneration and remodelling. To follow the effect of GC excesses on the negative feedback loop observed during a normal stress response on the pituitary gland, we stimulated adherent primary anterior pituitary colonies with dexamethasone and corticosterone. GC treatment led to downregulation of *Pomc* expression, a precursor polypeptide for ACTH and other hormones, in the treated colonies compared to the control. This downregulation caused by GCs could be mediated through different gene targets of the glucocorticoid receptor as well as via paracrine signalling from pituitary stem cells. Altogether, our results will provide us with more profound knowledge of mechanisms underlying interactions between stressors and stem/progenitor cells of the HPA axis along with novel therapeutic targets for stress-associated disorders.

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Perception of female patients with congenital adrenal hyperplasia and their parents on genital surgery: a retrospective survey

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Background
Congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CAH) is associated with ACTH-driven adrenal androgen excess. In women with classic CAH, this regularly causes prenatal virilisation of the external genitalia, commonly corrected by genital surgery during the first years of life. This practice, however, has been questioned and is discussed highly controversial. The aim of this study was to retrospectively assess the perspective of affected patients and their parents on genital surgery in CAH.
Methods
Adult female patients with classic CAH and their parents were enrolled in this single-center, cross-sectional, survey study. The patient's questionnaire included the female Sexual Function Index (fSFI; score 0-36) and female Sexual Quality of Life (SQOL-F; score 8-108) questionnaire, whilst the parent's questionnaire contained the Decision Regret Scale (DRS; score 0-100), with higher scores indicating better sexual function, better sexual quality of life or higher levels of regret.
Results
A total of 46 females with a mean age of 34.9 years (18-66) and 22 parents with a mean age of 60.5 years (47-80) were included in this study. All patients had classic CAH, 29 (63.0%) salt-wasting (SW), 17 (37.0%) simple-virilizing (SV) CAH. About half of the patients (45.7%) had undergone one genital surgery in their life, 52.2 % more than one. Most surgeries (60.9%) were performed up to the age of 5 years, 9.4% at 6-11 years, 21.9% at 12-17 years and 7.9% at 18 years and older. According to the patients, in 67.2% of cases, the decision to undergo surgery had been made by parents, in 3.8% of cases by the patients and in 19.2% of cases together. The fSFI was completed by 25 patients with a total median (IQR) score of 20.2 (5.7) the SQOL-F with a median (IQR) score of 93.0 (31.0) by 31 patients. There were no significant statistical differences between SW and SV patients in fSFI (18.4 (6.8) vs. 20.3 (4.5); $P = .177$) or SQOL-F (93.0 (52.6) vs. 94.0 (29.4); $P = .435$). Concerning the parents, 72.2 % showed no to mild regret concerning the decision of surgery (DRS 0-25) and 27.8% showed moderate to strong regret (DRS >26).
Conclusion
Female patients with classic CAH often undergo genital surgery at a young age, with their parents mostly responsible for treatment decisions. As adults, they present with sexual dysfunction whilst showing good sexual quality of life. Most parents have few or no regrets about the decision to have genital surgery performed on their children.

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Symptoms and Steroid Dose Adjustments Associated with the SARS-CoV-2 Vaccine in Patients with Adrenal Insufficiency

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Background
Following vaccination for SARS-CoV-2 a significant proportion of individuals experience moderate to severe symptoms. In patients with adrenal insufficiency (AI) this has been reported to translate in to need for increased glucocorticoids and incipient or frank adrenal crises. We assessed occurrence of symptoms, need for glucocorticoid dose adjustment and crises in a large cohort of patients with AI following vaccination for SARS-CoV-2.
Methods
Consecutive patients with AI completed a questionnaire relating to symptoms and steroid dose adjustments following both their 1st and 2nd SARS-CoV-2 vaccination. 14 common symptoms associated with the SARS-CoV-2 infection/vaccination were scored 0-10, with 10 being the most severe, providing a total symptom score of 0-140.
Results
290 consecutive patients completed the questionnaire (154 F; mean 57.9 [range 17 to 90] years; 38 PAI, 252 SAI). 145 (50%) documented a previous adrenal crisis within the previous five years. Fully completed questionnaires and data on 1st and 2nd vaccine received were available in 279. For the initial vaccine, 176, 100, & 3 received the Astra-Zeneca (AZ), Pfizer-BioNTech (PB) and Moderna (MD) vaccines respectively. For the second vaccine, 170, 99 &10 received the AZ, PB and MD vaccines respectively. The AZ vaccine had greater symptom burden compared with PB (17.7 +/-23.9 Vs. 11.3 +/-20.0; $P=0.001$). Younger age, female gender and previous adrenal crises correlated with higher symptom score after both 1st and 2nd vaccines ($P<0.05$). Total symptom burden was lower after the 2nd compared with the 1st for all vaccine subtypes. Symptom burden was not different in patients with PAI and SAI. Symptoms commenced a mean of 11.4 and 15.7 hours post-vaccine, lasting a mean of 58.9 and 49.2 hours for the 1st and 2nd vaccine dosage regardless of whether or not the steroid dose was increased. 34.8% and 31.4% increased their steroid dosage for a mean of 3.0 and 2.6 days following the first and second vaccines respectively. No difference in the proportion requiring dose increase was observed between PAI and SAI, or between genders. Patients with previous adrenal crises in the last five years were more likely to increase their steroid dosage. 3.1% (7AZ, 2PB) and 1.1% (2PB, 1MD) required an emergency hydrocortisone injection.
Conclusions
Around a third of patients with AI increased their steroid dosage to manage symptoms associated with the SARS-CoV-2 vaccination, however this was not different between vaccine subtypes despite differences in symptom burden. Few patients required an emergency hydrocortisone injection.

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Atorvastatin use is associated with decreased testosterone levels in type 2 diabetes men

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Introduction
Statins are used in the management of hypercholesterolemia and the prevention of cardiovascular diseases. However, by reducing cholesterol biosynthesis, steroidogenesis and particularly testosterone synthesis may be affected. The aim of our study was to assess the effect of high doses of statin therapy on testosterone levels in type 2 diabetes male patients.
Methods
This was a single-center, prospective study, during the period march 2021 - July 2022, including 60 men with type 2 diabetes mellitus, aged between 40 and 65 years, statin-free, and in whom the indication of a treatment with high dose of statin was indicated. The patients had two visits, before and six months after the daily intake of 40mg of atorvastatin. During each visit, they underwent a clinical examination including the Androgen Deficiency in the Aging Male (ADAM) questionnaire and a fasting blood sample was collected for biological and hormonal measurements including total testosterone, sex hormone binding globulin, and gonadotrophins.
Results
The median age was 58 years (IQR:52-62). The median duration of diabetes was 81 months (IQR: 26-132). The prevalence of a positive ADAM questionnaire increased from 73% to 85% after statin use ($P<10^{-3}$). Its median score raised from 4 (IQR: 2-6.75) to 6 (IQR: 3-8), $P<10^{-3}$. We noted a significant increase in the prevalence of a decreased libido from 22% to 47% and erectile dysfunction from 70% to 75% and a significant decrease in nocturnal erections and the frequency of sexual intercourses. Twenty-two patients developed gynecomastia. The median of total and calculated bioavailable and free testosterone significantly decreased from 15.1, 6.3, and 0.3 to 12.7, 5.7, and 0.2 respectively, with no change in FSH and LH levels. Three patients (5%) developed hypogonadism.
Conclusion
Long-term high dose statin therapy induced clinical symptoms of hypogonadism and a reduction in testosterone levels.

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Differences in the extracellular matrix protein signature of the outermost zone of the rat adrenal gland

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Changes in the composition of the extracellular matrix (ECM) induce different cell signaling in normal tissues and in pathological conditions. ECM alteration in the adrenal microenvironment may contribute to both the development and function of adrenal gland. The adrenal gland consists of a cortex, with three concentric zones, glomerulosa (ZG), fasciculata (ZF) and reticularis (ZR), and the medulla (M), surrounded by a capsule. Here, we describe the differences among the ECM signatures of fractions obtained from rat adrenal glands, the outer fraction (OF), the inner fraction (IF) and the medulla (M). Sprague-Dawley rats (250 $\pm$30g, $n=6$) were euthanized by decapitation and adrenal glands were removed and decapsulated to separate the capsule/zona glomerulosa (OF) from the zona fasciculata/reticularis (IF) followed by removal of medulla (M). The samples were frozen in liquid nitrogen and stored at -80°C. ECM enrichment through decellularization was achieved through incubation in 1% Triton-X for 2h30 min at room temperature following incubation in 4.0% deoxycholate until complete decellularization. The absence of remaining intact cells was certified by DNA quantification and microscopy analysis of decellularized tissues stained with DAPI. Pellets containing ECM proteins were treated as described in Trombetta-Lima et al. (J. Proteome Res. 2021, 20, 4693-4707). We compared the proteomic profiles of OF, IF and M fractions samples ($n=6$). Raw files of LC-MS/MS were processed into MaxQuant software version 2.1.4 using Andromeda search engine against SwissProt *Ratus norvegicus* and *Mus musculus* combined databases (54,778 and 17,121 entries, respectively, downloaded from Uniprot.org November 2022). The total identified and regulated proteins were compared with MatrisomeDB 2.0. Our analysis revealed that 69, 144 and 121 total proteins were detected in OF, IF and M decellularized fractions, respectively. Ninety-two proteins were identified as common to the OF, IF and M fractions, 23 of which are ECM proteins. Among the total proteins from adrenal fractions analyzed, 89 were regulated proteins, 22 of which are ECM proteins. Four proteins were differentially expressed in the OF, 22 in the IF and 8 in the M. Only the OF showed 3 differentially expressed ECM proteins, which are Fibrillin 2 (Fbn2), Collagen XIV alfa1 (Col14a1) and Collagen IV alfa3 (Col4a3) which will be validated by immunoblotting and immunohistochemistry. Therefore, we report differences in ECM composition of the outermost zone of rat adrenal that may influence adrenal pathophysiology.

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ARMC5 regulates SIRT1 expression in adrenocortical cells

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Pathogenic *ARMC5* variants are the main genetic cause of Primary Bilateral Macronodular Adrenal Hyperplasia (PBMAH) explaining roughly 20% of index cases. These variants found both at germline and somatic level are mostly

frameshift and nonsense leading to a loss of its function. *ARMC5* acts then, as a tumor suppressor gene but little was initially known on its function. Using an RNAseq analysis on transient zebrafish models of *Armc5* up- and down-regulation, we identified transcriptional alterations of several members of SIRT1 signaling in our models suggesting that ARMC5 may regulate the desacetylase SIRT1 and its signaling in adrenocortical cells. Consistently, there is a significant increase of SIRT1 protein in PBMAH tissues mutated for *ARMC5* compared to PBMAH without known genetic alterations. Interestingly, we show that ARMC5 interacts with SIRT1 in the H295R human adrenocortical cells and that *ARMC5* knockdown leads to a decrease of SIRT1 ubiquitination. These results are consistent with 2022 reports demonstrating that ARMC5 acts as a protein adaptor for Cullin 3 complex, recruiting protein substrate to be ubiquitinated by this complex in order to lead to their proteosomal degradation. We speculate that SIRT1 could be a new protein substrate for the Cullin3-ARMC5 complex. While we analyze the global protein acethylation profile in PBMAH tissues, we observe an elevation of acetylated protein in absence of *ARMC5* suggesting either a global reduction of protein desacethylation or increase of acethylation. To access more specifically the potential consequence of *ARMC5* loss on SIRT1 activity, we measure SIRT activity and demonstrate a decrease of its activity in PBMAH mutated for *ARMC5* as well as in adrenal cells of 18-month-old *Armc5*$^{+/-}$ mice presenting an elevation of plasma corticosterone level. The decrease of SIRT1 activity leading to an abnormal protein acetylation could then, play a role in the development of PBMAH and in the cortisol hypersecretion. Altogether, these data support that ARMC5 could regulate SIRT1 protein accumulation (possibly through the Cullin3 complex) but could also regulate its activity by a mechanism that remains to be determined.

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Significance of exogenous estradiol on plasma cortisol during ACTH stimulation in women with pituitary insufficiency

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Objective
Exogenous estradiol increases cortisol binding globulin (CBG) and total cortisol (TC), and therefore it is debated if estradiol supplementation should be paused before evaluation of the adrenal axis. The aim was to evaluate how oral and transdermal estradiol influence TC in hypogonadal women with, or at risk of developing, adrenal insufficiency (AI)
Methods
This was a crossover study in 17 women with secondary hypogonadism who were tested without estradiol (baseline) and after 12 weeks on oral estradiol (2 mg) and transdermal estradiol (100 µg/day). At the end of the interventions, the following samples were measured: salivary cortisol, p-cortisol, s-CBG, and other pituitary hormones and binding proteins. Afterwards, a short 30 minute ACTH stimulation test was performed with a TC cut-off threshold for AI of 420 nmol/l.
Results
Estradiol levels were significantly higher on oral (0.45 (0.28-0.65) and transdermal estadiol (0.27 (0.09-0.44) compared to baseline (0.09 (0.09-0.09) nmol/l), $P<0.005$. Plasma SHBG was higher on oral vs. transdermal estradiol (92 ± 36 vs 48 ± 17 nmol/l, $P<0.001$). TC before ACTH stimulation was 124 (27-311) at baseline, 105 (15-262) on transdermal and 201 (26-315) nmol/l on oral estradiol, $P=0.015$. TC after ACTH stimulation parallels that of baseline cortisol, but without any significant changes; baseline 309 (54-492), transdermal estradiol 304 (48-492) and oral estradiol 440 (74-600) nmol/l. Three participants crossed the TC cut-off threshold for AI between interventions: Patient 1: 401 at baseline vs. 442 on transdermal vs. 487 nmol/l on oral estradiol. Patient 2: 423 at baseline vs. 390 on transdermal vs. 490 nmol/l on oral estradiol. Patient 3: 395 on transdermal vs. 559 nmol/l on oral estadiol (the patient did not complete the no intervention period). Data on CBG and salivary cortisol are under preparation.
Conclusion
In opposite to oral estradiol transdermal estradiol did not influence the adrenal axis. In patients with overt AI TC was not influenced by oral estradiol. Thus, a diagnosis of severe AI can probably not be missed if ACTH test is performed in patients on oral estradiol. Three of 17 patients with borderline AI changed status from insufficient to sufficient when put on oral estradiol. Adrenal testes independent of CBG levels are warranted to secure reliable results during conditions with altered plasma CBG and to avoid inconvenient pause of gonadal substitution. Measurement of salivary cortisol or CBG might be away to move forward, and these data will soon be available in the present study.

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Modulation of calcium signaling 'on demand' in adrenocortical cells to decipher the molecular mechanisms responsible for primary aldosteronism

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Introduction
Primary aldosteronism (PA) is the most frequent form of secondary hypertension. Over the past 10 years, important discoveries have been made regarding the genetic basis of aldosterone producing adenoma and familial forms of primary aldosteronism. In most cases, genetic abnormalities are found in genes coding for ion channels (*KCNJ5, CACNA1D, CACNA1H, CLCN2*) and pumps (*ATP1A1, ATP2B3*). These mutations affect intracellular ion homeostasis and/or cell membrane potential, leading to increased intracellular calcium concentrations and activation of calcium signalling, which is the main regulator of aldosterone biosynthesis.
Objective
The objective of our work was to elucidate, using chemogenetic tools, the molecular mechanisms underlying the development of PA by modulating sodium entry into the cells, thus mimicking some of the known mutations identified in PA.
Methods
We have developed an adrenocortical H295R-S2 cell line stably expressing a chimeric ion channel receptor formed by the extracellular ligand-binding domain of the α7 nicotinic acetylcholine receptor fused to the ion pore domain of the serotonin receptor 5HT3α named α7-5HT3. Its activation by a selective agonist named PSEM-817 leads to sodium entry into the cells. This cell line was characterized in terms of intracellular calcium concentrations, cell proliferation, steroid production, electrophysiological properties and gene expression.
Results
Treatment of α7-5HT3 expressing cells with increasing concentrations of PSEM-817 (from 10^{-9} to 10^{-5} M) induced significant cell membrane depolarization, leading to the opening of voltage gated calcium channel and increased intracellular calcium concentrations. Activation of calcium signaling resulted in increased *CYP11B2* (coding for aldosterone synthase) mRNA expression and aldosterone biosynthesis but did not affect cell proliferation measured at different time points (8h, 24h, 48h, 72h). Interestingly, calcium kinetics analyses revealed significant differences in response to treatment with PSEM-817, which leads to sodium entry into cells, or with potassium. Gene expression analyses, by RNA sequencing, revealed the activation of different specific signaling pathways in response to treatment with Angiotensin II, potassium and PSEM-817.
Conclusions
Our results suggest that modulation of intracellular sodium concentrations may activate specific signaling pathways, different from those induced by angiotensin II and potassium. This cell line, in which we can modulate the intracellular calcium concentration 'on demand' through modulation of sodium entry into the cells, is a useful tool for a better understanding of the alterations of intracellular ion balance and calcium signaling in the pathophysiology of PA.

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Relative adrenal insufficiency in liver cirrhosis: a common but often forgotten critical condition

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Introduction
Relative adrenal insufficiency (RAI) is common in critically ill patients and is characterized by the normal adrenal reserve for homeostatic demands and inadequate cortisol response in acute stress situations. RAI can also occur in

patients with liver cirrhosis, both compensated and decompensated. However, it is often forgotten and difficult to diagnose due to the overlap between clinical symptoms of adrenal insufficiency and decompensated liver disease. Also, hypothalamic pituitary adrenal axis analysis in patients with cirrhosis is not performed routinely so many of these cases remain undiagnosed or misdiagnosed.
Case report
A male patient, 54 years of age, was admitted to Hepatology Department, Clinic for Gastroenterology and Hepatology due to a alcoholic liver cirrhosis (Child B) with esophageal varices grade 2/3 and refractory ascites. He was initially diagnosed in 2017 and had daily ascites drainage through permanent peritoneal catheter placed in his regional medical centre in 2021. At admission, he complained of abdominal pain, fatigue, nausea and diarrhea. Biochemical and hormonal evaluation showed hyponatremia 124 mmol/l, hyperkalemia 5.9 mmol/l, normal renal function, very low cholesterol 2.08 mmol/l, high TSH 13 mIU/L, with low fT4 8.1 pmol/l, low ACTH 0.6 pmol/l with low-normal cortisol 233 nmol/l, which is why he was sent for an endocrinological evaluation. In the physical examination, the patient was awake, communicative, afebrile, and hypotensive with no signs of haemorrhagic syndrome and besides hypotension of 80/50 mmHg, no other typical clinical sign of hypocortisolism. Based on electrolyte status, low ACTH, low normal cortisol and hypotension the Synacthen test was performed which showed an inadequate cortisol response: 237 nmol/l (0 min), 323 nmol/l (30 min) and 385 nmol/l (60 min). Hydrocortisone treatment was initiated and after two days all reported complaints resolved along with electrolyte and blood pressure normalization. Also, levothyroxine supplementation was initiated.
Conclusion
Diagnosis and treatment of RAI in cirrhotic patients remains controversial. Empiric glucocorticoid treatment is not recommended in asymptomatic patients. However, patients who are symptomatic benefit from glucocorticoid replacement as it was the case in our patient. These patients should have a close and careful follow up for sings of cortisol overtreatment and/or infection.

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Metastatic composite pheochromocytoma manifesting as severe bone pain

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Composite pheochromocytomas (CP) are rare and constitute 3% of pheochromocytomas. So far, less than 100 cases were described in the literature. We present a case of 60 years old man. He was admitted to ER department due to severe bone pain around chest, ribs and vertebra. CT scan showed expansive, 100x87 mm, non-homogenic left adrenal gland tumour as well as metastatic bone lesions. The 24-hour urinary fractionated metanephrines were significantly elevated - 86195 ug/24h (normal range:88,0-440,0), 10214,1ug/24h (normal range:0,0-220,0) and 3302,4 ug/24h (52,0-341,0) for urinary fractionated normetanephrine, 3-methoxytyramine, and metanephrine, respectively. Patient presented no typical symptoms suggestive of pheochromocytoma like hypertension or tachycardia. Tc-99m somatostatin analogues scintigraphy revealed pathological tracer uptake in the left adrenal gland and bones. Patient underwent left adrenalectomy preceding by pharmacological pre-treatment with alpha-receptor blockers. Histopathology showed composite pheochromocytoma with ganglioneuroma component (Ki67 15%, PASS 9). Due to results of MIBG scan, which showed massive bone metastases, patient was qualified for stem cells preservation followed by radioisotope therapy (I-131 MIBG). Initial genetic testing (MAX, RET, SDHB/SDHD, VHL, MEN1) didn't confirm genetic background, further genetic testing results (TMEM, EPAS FH, SDHA, SDHAF2) are expected. In conclusion, metastatic potential of pheochromocytoma in this case should be suspected based on large tumour dimension (> 6 cm), secretion of norepinephrine and dopamine, as well as distinct histological features (Ki67>3%, PASS>6). Due to its rarity, it is not well known if non-pheochromocytoma component in CP poses any prognostic factor, which needs further investigations.

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Cardiometabolic and Kidney Biomarker Effects of Gender-affirming Hormone Therapy in Transgender Males

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Introduction
Testosterone-based gender-affirming hormone therapy (GAHT) may have negative consequences on cardiovascular risk, with reported increased blood pressure, decreased HDL-cholesterol, and weight gain. Still, data on cardiometabolic changes in transgender men on GAHT remain controversial. Testosterone-based GAHT also modifies body composition and lean muscle mass, but the degree to which affects serum creatinine and other measures of kidney function is still not clear.
Objectives
To characterize the change in cardiometabolic risk factors (blood pressure, weight, lipid profile) and serum creatinine in transgender people initiating masculinizing GAHT.
Methods
Single-centre retrospective study, including a cohort of 60 transgender males, with follow-up between 2015-2022. Data collection was performed before and after one year of initiating GAHT and included levels of total-cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and serum creatinine; blood pressure and weight. Estimated glomerular filtration rate (eGFR) was calculated based on CKD-EPI equation for cisgender. We excluded people: with previous renal failure or dyslipidemia; under therapies with influence on lipid profile/renal function; submitted to ovariectomy.
Results
Transgender males average age was 22.5 $\pm$6.7 years. Prescribed GAHT consisted of testosterone enanthate/cypionate, monthly average dose 290 $\pm$60mg. After 12 months of GAHT, there were no significant changes on weight or blood pressure. Regarding lipid profile, there was a decrease in HDL-cholesterol (-7.6mg/dL, IC 95% [-13.5;-1.7]), increase in triglycerides (+ 12.5mg/dL, IC 95% [0.2;24.9]), and increase in LDL-cholesterol (+ 14.1mg/dL, IC 95% [4.8;23.5]). We also found an increase in serum creatinine (+ 0.110 mg/dL, IC 95% [0.078;0.142]) and a reduction in eGFR (-16.0 ml/min/1.73m^2, IC 95% [-20.0;-12.0]). In a univariate regression model adjusted for testosterone dose and weight, we found significant changes in HDL-cholesterol (-7.8 mg/dL, $P = 0.027$, $r = 0.153$) and serum creatinine (+ 0.101 mg/dL, $P < 0.001$, $r = 0.307$).
Conclusion
We observed an unfavorable trend in lipid profile in transgender males after one year of GAHT. Healthcare professionals should monitor and discuss lifestyle interventions and pharmacological therapy with patients who are at risk of developing cardiovascular disease. Serum creatinine also changed, resulting in a decreased eGFR. However, this presumably may reflect the corresponding increase in muscle mass, rather than a true change in GFR. Our results raise the question of how to estimate GFR based on equations in transgender people, as one of the variables is gender, and serum creatinine is affected by GAHT.

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Safe observation of early recurrence of asymptomatic pheochromocytomas in MEN2 patients

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Controlateral recurrence of pheochromocytoma is frequent in MEN2 patients. Cortical sparing adrenalectomy is currently recommended in this situation, but conveys a risk of adrenal insufficiency in up to 45 % of patients. The natural history of recurrent pheochromocytome is poorly known. Thus, appropriate timing of surgery and the possibility to postpone safely surgery remain debatable. We report our experience of long-term follow up of non-operated 16 pheochromocytomas in 13 MEN2 carriers. At diagnosis of MEN2 pheochromocytoma, 11/13 patients were normotensive and 2 were treated with calcic inhibitors. 7/13 had normal metanephrines values, contrasting with abnormal imaging studies. 6/13 had a median metanephrine level of 1.8 x ULN (range : 1.1 – 4.0 x ULN). Median tumor size at diagnosis was 12 mm (range : 8 – 24 mm). During follow-up (median duration of follow-up 5 years ; range : 2 – 26 years), median tumor growth was 0.5 mm/year (range : 0 – 2.1 mm/year). Among the 7 initially 'non-secreting' patients, metanephrine levels increased from 1.2 to 4.6 x ULN in 5 patients and remained normal in 2 patients. Among the initially 'secreting' patients, metanephrines increased from 1.8 to 4.6 x ULN. Tumor growth and metanephrine increments were correlated ($r = 0.8$, $P < 0.01$). No hypertension was reported in initially normotensive patients. No morbid cardiovascular event occurred in any patient. Surgery of 7/16 pheochromocytomas was performed after 2 to 26 years of follow-up. The reasons were : occurrence of mild symptoms (heart palpitations) in 4

patients, absence of previous contralateral surgery in 3 patients. Despite delaying surgery, parameters of per-operative hemodynamic instability were significantly milder than those of a control group of hypertensive sporadic pheochromocytomas ($P<0.05$).

Conclusion

tumoral and secretory progression is slow in MEN2 pheochromocytomas. In early-stage, asymptomatic recurrence, a careful follow-up allows to postpone safely complementary surgery and its attendant risk of adrenal insufficiency.

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Pheochromocytomas in patients with Parkinson's disease: a diagnostic and therapeutic challenge

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Dopamine agonists can falsely elevate plasma and urinary metanephrines, thus making the diagnosis of pheochromocytomas in patients taking these medications challenging. We present the case of an 80-year-old female care home resident with a background of hypertension, Parkinson's disease (PD), dementia and pernicious anaemia. She presented with weight loss, unilateral leg swelling and abdominal distension. A computed tomography (CT) showed a 5.6 cm heterogeneously enhancing left adrenal mass. The patient reported no symptoms consistent with a phaeochromocytoma and the physical examination revealed no stigmata of an endocrinopathy. Biochemistry showed significantly raised plasma metanephrine, normetanephrine and 3-methoxytyramine, favouring the diagnosis of a pheochromocytoma over a false positive result due to carbidopa/levodopa. Urinary metanephrines were also high and an iodine-123 metaiodobenzylguanidine (MIBG) scan revealed increased radiotracer uptake in the left adrenal, confirming the diagnosis. Surgical treatment was discussed with the patient and her daughter and in view of significant frailty, comorbidities, high surgical risk and absence of symptoms, it was pragmatically agreed to manage her conservatively. Medical treatment with alpha blockers followed by beta blockers was not thought to be in her best interest due to risk of postural hypotension and falls in presence of PD and because blood pressure was well controlled on ramipril. An interval CT scan did not show any change in the size or characteristics of the lesion, further supporting conservative management. She is currently being followed up in the endocrine clinic. This case emphasises the need to interpret measurements of catecholamines and their metabolites in the context of confounding medications like carbidopa/levodopa, which can falsely elevate plasma and urine metanephrines, especially 3-methoxythyramine and urinary dopamine. Clinicians need to be mindful of such a pitfall, not rely on biochemical or radiological diagnosis only and consider early functional imaging with MIBG scintigraphy, gallium-68 DOTATATE positron emission tomography (PET) or fludeoxyglucose-PET, amongst others. We suspect that our patient's lesion grew to such a large size due to her lack of hormone-related symptoms as symptomatic phaeochromocytomas are often diagnosed when relatively smaller. Apart from a diagnostic challenge, patients with PD and other comorbidities can also be challenging to manage, as they are often high-risk surgical candidates, and adrenalectomy, which would otherwise be a gold standard curative treatment, is not an option. Shared decision making, multidisciplinary team approach with a view to provide individualised, holistic care and good communication with patients and their families are key elements in management.

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Differentiation of Pluripotent Stem Cells into Steroidogenic Cells with the Application of Artificial Intelligence

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Adrenal insufficiency is a life-threatening condition in which the adrenal glands fail to produce adequate amounts of steroid hormones thus leading to severe disturbances of body homeostasis. Today's treatment options are limited to hormone replacement therapies that are, however, hampered by serious side effects. Cell replacement therapies with adrenocortical stem cells could present a potential cure, but the culture of such stem cells has proven difficult. We have developed an *in vitro* protocol for the differentiation of mESCs into adrenocortical steroidogenic cells. Our protocol recapitulates key steps in embryonic development by fating the cells towards the adrenal primordium. Molecular analysis demonstrated upregulation of fetal adrenal markers and the expression of genes coding for adrenal cortex specific steroidogenic enzymes (e.g. *Cyp21A1*). Indeed, steroidomics profiling revealed the secretion of adrenal cortex specific steroid hormones into the culture medium. The proportion of steroidogenic cells produced in our differentiation protocol remained, however, relatively low for therapeutic purposes. Machine Learning (ML) has been shown to be a powerful tool for improving the interpretation of biological data (1,2). To improve culture conditions and increase the yield of properly differentiated cells, we aim to apply ML methods to our *in vitro* differentiation protocol. In pilot studies, a VGG-16 convolutional neural network followed by random forest classification was employed to distinguish phase contrast images from different stages of differentiating cells based on their morphology. Indeed, we were able to distinguish cells based on the treatment they had received and to predict their differentiation. We are currently planning to optimize our *in vitro* differentiation protocol by taking into consideration the input from the ML model. In the future, we will incorporate more molecular data to increase our prediction accuracy (3). Once high yields of differentiated adrenocortical cells have been obtained, they will be tested for long term engraftment and hormone production *in vivo* (transplantation experiments). Taken together, we have generated glucocorticoid producing adrenocortical cells from pluripotent stem cells *in vitro*. In the long run, our protocols may pave the way for the development of cell replacement therapies for patients suffering from adrenal insufficiencies.

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P550

Is there any link between non-classic adrenal hyperplasia (NCAH) and glucose metabolism?

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Introduction

There are data reporting an increased risk of cardiovascular and metabolic complications in patients with NCAH. This is frequently attributed to glucocorticoid (over)use. It seems that long-term exposure to increased androgens concentration may also itself lead to diminished insulin sensitivity and increased risk of prediabetes and diabetes.

Aim

The aim of the study was to assess the link between NCAH diagnosis and glucose metabolism disturbances.

Material and methods

The study included 327 subjects (315 females and 12 males, median age 25 years) referred for a cosyntropin stimulation test due to the suspected NCAH. Serum 17-OH-progesterone (17-OHP) was measured with ELISA assay. The diagnosis of NCAH was confirmed if the initial or stimulated 17-OHP concentration exceeded 10.0 ng/ml. None of the tested subjects was treated with glucocorticoids. The Mann-Whitney U and Yates' $\chi 2$ tests were used in statistical analyses, with $P<0.05$ as cut-off value of statistical significance.

Results

62 patients (60 females, 2 males; median age 26 years) were diagnosed with NCAH, the rest of tested subjects were considered the control group. Type 2 diabetes was diagnosed earlier in 10 subjects in the entire study group (6 of them were diagnosed with NCAH). There was no significant difference in the fasting glucose levels ($P=0.08$) and BMI ($P=0.32$) between subjects with and without NCAH diagnosis (median fasting glucose: 4.96 mmol/l and 4.86 mmol/l, respectively; median BMI: 23.82 kg/m^2 and 23.26 kg/m^2, respectively). Diabetes was significantly more frequent in patients with NCAH diagnosis ($P=0.004$; power: 0.74). The median 17-OHP was higher in patients with diabetes compared to those without it at both 30 (12.25 ng/ml vs 3.25 ng/ml; $P=0.003$) and 60 minutes (14.93 ng/ml vs 3.95 ng/ml; $P=0.046$) after stimulation.

Conclusions

NCAH seems to be linked to increased diabetes risk, even before glucocorticoid treatment is initiated. It seems advisable to screen NCAH patients for glucose metabolism disorders.

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P551

Does this patient really have a pheochromocytoma? A retrospective analysis of patients undergoing adrenalectomy overdiagnosed with pheochromocytoma

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Background
Pheochromocytoma and paraganglioma (PPGL) are rare endocrine tumours that secrete catecholamines. Methoxycatecholamines in free plasma or fractionated methoxycatecholamines in 24-hour urine collections are the recommended tests for the diagnosis of pheochromocytoma, based on which patients are referred for surgical removal of the adrenal gland. However, false-positive results from these tests remain a problem and some patients are referred for adrenalectomy due to suspected pheochromocytoma, but the verifying histopathological examination does not confirm the diagnosis.
Aim
The aim of the study was to assess the characteristics of patients overdiagnosed as pheochromocytoma and undergoing treatment with adrenalectomy.
Methods
Data from 107 adult patients, who underwent laparoscopic adrenalectomy for suspected pheochromocytoma between January 2012 and December 2022, were retrospectively analysed. The patients were divided into two groups: the first, in which the postoperative histopathological examination confirmed the diagnosis of pheochromocytoma ($n=74$), and the second, in which the suspicion of pheochromocytoma was not confirmed ($n=33$).
Results
Following histopathological examination of the postoperative material, the diagnosis for 30.8% of the tumours clinically suspected as pheochromocytoma was reclassified. The tumours that were most frequently over-diagnosed as pheochromocytomas were adrenocortical adenomas ($n=16$) and adrenocortical hyperplasia ($n=10$). In addition, 3 adrenocortical carcinomas, 1 oncocytic tumour, 1 myelolipoma, 1 metastatic neuroendocrine carcinoma and 1 completely normal adrenal gland were misclassified as pheochromocytoma. Patients with histopathologically confirmed pheochromocytoma were younger (median 56, IQR 23 years vs median 63, IQR 8 years, $P=0.027$) and had a lower BMI (median 26, IQR 6.4 kg/m^2 vs median 29.6, IQR 7.6 kg/m^2, $P<0.001$). In addition, patients with pheochromocytomas had significantly higher concentrations of metanephrine (median 1119.5, IQR 2868 vs median 175.2, IQR 136 µL/24 h, $P<0.0001$) and normetanephrine (median 4399.4, IQR 4703 vs median 659.73, IQR 501.9 µL/24 h, $P<0.0001$) determined in the daily urine collection. There were no statistically significant differences between tumours histopathologically confirmed as pheochromocytoma and false-positive pheochromocytoma with regard to sex, methoxytyramine levels, morning and evening cortisol levels, aldosterone, plasma renin activity, adrenocorticotropic hormone. The size of the adrenal gland on preoperative CT scan and the size of the tumour on histopathology were also not significantly different between groups.
Conclusions
There is still a considerable number of patients undergoing adrenalectomy for suspected pheochromocytoma in whom histopathological verification does not confirm the initial diagnosis. A significant proportion of these are benign tumours that do not need surgical treatment.

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Non-specific uptake of magnetic iron oxide nanoparticles by Adrenocortical carcinoma and Endothelial cells

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Adrenocortical carcinoma is a rare malignant tumour that starts in the adrenal gland, accounting for 4% of all adrenal tumours. Functioning ACC can cause symptoms related to the overproduction of hormones and large tumours can press on nearby organs. Primary treatment for ACC tumour is surgery to remove the tumour, and may also include Chemotherapy or Radiation to stop the cancer cells from spreading. Therefore, more affective therapies for delivering therapeutics to the tumour are highly desirable. Magnetic iron oxide nanoparticles (MIONPs) have been gaining traction over the years for treatment of various cancers as they can be produced in various shapes and sizes, with the ability to modify the surface by coating the nanoparticles. Hence, MIONP delivered chemotherapy with associated hyperthermia has become an area of great interest. In this study, MIONPs have been used at different concentrations to evaluate non-specific nanoparticle uptake and rate of uptake by adrenal cortical and endothelial cells, as well as gain understanding of the location of nanoparticles within the cell. MIONPs were provided by The University of Kansas. Adrenal Cortical cell-lines (MUC1, H295R and HAC15) and Endothelial cell-line (HUVEC) were used in this study. Cells were incubated with MIONPs were for 24 h at concentrations ranging from 0.5 to 50 µg/ml. MIONP uptake, rate of uptake and vaibility was assessed by Flow Cytometry. Confocal Microscopy was used to image cellular morphology, and live imaging was carried out to view live uptake. Cellular proliferation was assessed by Ki-67. "Seahorse" technology was used to assess the effect of MIONPs on mitochondrial acttivity. Intracellular location of MIONPs was visualused TEM. The effect on steroidogenesis in the presence of MIONPs was assessed by Mass Spectrometry. Steroidogenic enzyme expression was assessed by RT-PCR. Viability, the location of MIONPs and proliferation post 7 days were assessed by Flow Cytometry, TEM and Ki-67. Following 24 hour incubation, Flow Cytometry showed significant uptake by Adrenocortical and Endothelial cells at 10 µg/ml MIONP concentration. Confocal and TEM images revealed MIONPs reside in the cytoplasm and in the vesicles of the cells. Live Confocal imaging showed movement of HAC15 cells towards MIONPs for phagocytosis. We demonstrated that ACC cells uptake MIONPs in a time and dose dependent manner. MIONP concentration from 0.5 to 10 µg/ml showed no cytotoxic affect, while cytotoxic affect was observed at 50 µg/ml. 10 µg/ml MIONP concentration was deemed optimal for ACC and Endothelial cells.

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Cushingoid features in a patient with adrenal insufficiency secondary to combined inhaled steroid and Itraconazole therapy

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Background
Iatrogenic adrenal insufficiency (AI) refers to primary, secondary, or tertiary hypoadrenalism associated with drug administration, surgery, or irradiation. The most common cause of secondary adrenal insufficiency is exogenous glucocorticoids. Hepatic metabolism of inhaled corticosteroids (ICS) takes place via cytochrome P450 3A4. Nevertheless, it can be decreased by enzyme inhibitors such as itraconazole or ritonavir, thus leading to an increase in the bioavailability of ICS. This can result in an accumulation of the steroid drug and a Cushing's syndrome whilst also leading to suppression of adrenocorticotropic hormone (ACTH) and hypoadrenalism. We report here a case of coexisting secondary adrenal insufficiency and iatrogenic Cushings syndrome from combined inhaled steroid therapy and Itraconazole.
Case
A 45-year-old female with known bronchiectasis, childhood asthma, atopic eczema and Allergic bronchopulmonary aspergillosis (ABPA) was taking Itraconazole 200mg twice daily for her ABPA for over three years. In addition, she was also on combined therapy with Symbicort (budesonide /formoterol) 200/6 inhaler, Mometasone 50 mg nasal spray and topical Hydrocortisone 1% cream. She presented to her general practitioner initially with a few months' history of fragile, paper-thin skin and developing easy bruising. She had also had central weight gain and had developed puffy, rounded facial features. Her symptoms had progressively worsened over the previous one year. Her initial investigations were two 9am serum cortisol levels of <28 nmol/l. An ACTH stimulation (Short Synacthen) Test demonstrated both basal and 30 minute cortisol values of <28nmol/l. Her combined therapy was complicated by profound adrenal shutdown and impairment of inhaled steroid clearance which resulted in paradoxical Cushingoid features.

Discussion
This case emphasises the importance of considering assessing the hypothalamic-pituitary-adrenal-axis, when considering combined therapy with Itraconazole and inhaled steroid treatment. Clinicians should be aware of the potential occurrence of iatrogenic Cushing syndrome and secondary adrenal insufficiency due to the association of inhaled corticosteroids with itraconazole.

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P554

Unexpected cause of hypertension associated with hypokalemia

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Background
Prolonged ingestion of licorice has been known to cause hypokalemia and resistant hypertension amongst other disturbances. This is due to glycyrrhizin that inhibits the 11-β-hydroxysteroid dehydrogenase enzyme type 2 which results into increased plasma cortisol levels that stimulate the mineralocorticoid receptors resulting into apparent mineralocorticoid excess.
Case report
A 45-year-old woman resident in an iodine sufficient area, heavy smoker, was referred by her cardiologist to a tertiary endocrine center due to uncontrolled hypertension, for the past 4-5 years, with maximum systolic blood pressure of 200 mmHg, a transient paresthesia episode and hypokalemia. She denied any headaches, sweating, tremors or pallor, but was affirming rapid heartbeats. Physical examination revealed normal body mass index, regular heart rhythm with H $r=80$/min, blood pressure of 145/80 mmHg in clinostatism with 140/80 mmHg in orthostatism and no reddish-purple striae. Biochemical assessment revealed moderate anemia, moderate hypokalemia (K= 2.9 mmol/l), eunatremia (Na= 142 mmol/l). The ECG showed flattened T-waves. After 30 mEq KCl iv and oral potassium supplementation her K levels increased to 3.2 mmol/l). Hormonal assessment revealed a low-renin hypertension: mineralocorticoid axis after 2 h of standing and 5-15 minutes of sitting showed plasma aldosterone at the lower limit of normal (29.3 pg/ml) and suppressed direct plasma renin (= 1.92 pg/ml - 4 days after stopping beta blocker treatment), with aldosterone/renin ratio= 1.52 ng/dl/ng/l (non-diagnostic for primary aldosteronism). Glucocorticoid axis, plasma catecholamines (plasma metanephrines= 33.7 pg/ml, plasma normetanephrines= 82 pg/ml), thyroid function, PTH and IGF1 levels were normal. Abdominal ultrasound was unremarkable, however the native computed tomography revealed right adrenal hyperplasia. Upon a thorough dietary history, the patient stated that she was ingesting, for the past 20 years, licorice based candies in excessive amounts (around 160 grams/day). She was discharged with oral potassium supplementation, 10 mg of Amlodipine daily and the indication to withdraw all licorice candies ingestion.
Follow-up
One month after licorice withdrawal, serum potassium level was normal (4.5 mmol/l) without any supplements and blood pressure normalized.
Conclusion
This case highlights the importance of dietary history in patients with hypertension, hypokalemia and hormonal picture of pseudohyperaldosteronism. Apparent mineralocorticoid excess due to increased licorice ingestion should be considered for differential diagnosis of secondary hypertension.

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Coagulation parameters in patients with adrenal incidentalomas and mild cortisol secretion: sex difference matters

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Background
Patients with Cushing's syndrome (CS) typically show an alteration in the intrinsic coagulation pathway, leading to an increased risk of venous thromboembolism. Cortisol autonomy has been variably associated with higher risk of cardiovascular events and mortality compared to patients with non-functioning adrenal adenomas (NFA), particularly in women younger than 65 years. However, dedicated studies describing coagulation status in patients with adrenal incidentaloma are lacking.
Aim
To describe the effects of cortisol autonomy (defined as non-suppressible serum cortisol on dexamethasone-suppression testing, DST) on coagulation parameters in patients with adrenal incidentaloma enrolled in the ITACA study (NCT04127552) and to investigate sex differences.
Methods
A prospective study on 90 asymptomatic patients with adrenal incidentaloma was performed (62% female, mean age 62 ± 10). Patients with clinically apparent hormonal excess, active malignancy, history of thrombosis or taking hormone replacement therapy and anticoagulants were excluded. According to DST, three groups were defined: 41 NFA (<50 nmol/l), 39 possible autonomous cortisol secretion (PACS, 50 to 138 nmol/l) and 10 ACS (>138 nmol/l). Coagulation markers (fVIII, fVII, fV, fibrinogen, PT, aPTT, platelets) and coagulation inhibitors (Antithrombin III, Protein C, Protein S) were evaluated.
Results
A weak positive correlation was found between DST and platelets ($r=0.217$; $P=0.042$). Nevertheless, no differences in coagulation markers and inhibitors were observed among the three groups. A sub-group analysis by sex was performed in PACS and NFA groups. In PACS group, females compared with males had significantly decreased levels of aPTT ($aPTT_{Female}$ 28.7 sec ± 2.7 *vs* $aPTT_{Male}$ 32.1 sec ± 4.7, $P<0.01$) and increased levels of fVIII ($fVIII_{Female}$ 155% [125-163] *vs* $fVIII_{Male}$ 117% [95-121], $P=0.037$), fibrinogen ($fibrinogen_{Female}$ 3.67 g/l [2.62-4.60] *vs* $fibrinogen_{Male}$ 2.98 g/l [2.42-3.39] $P=0.018$), ATIII ($ATIII_{Female}$ 106.5% ± 12.5 *vs* $ATIII_{Male}$ 91.8% ± 5.5, $P<0.01$) and Protein C ($Protein\ C_{Female}$ 138% [117-149] *vs* $Protein\ C_{Male}$ 109% [87-129], $P=0.039$). Moreover, the frequency to have altered fVIII levels was greater in females than in males (81.2% *vs* 18.8%; OR 4.33, 95%CI 0.94 to 20.03, $P=0.05$). No sex differences were found in NFA group.
Conclusion
Overall, asymptomatic patients with adrenal incidentaloma, seem not to show alterations in coagulation parameters, in contrast to patients with overt CS. However, considering the presence of sex differences in coagulation markers and inhibitors, females with adrenal adenoma show alterations in coagulation pathways, especially those with a DST >50 nmol/l who therefore might benefit, in selected cases, from anticoagulation prophylaxis before and after adrenal surgery.

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P556

Cardiometabolic and bone health in postmenopausal women with glucocorticoid replacement therapy due to adrenal insufficiency; where do we stand

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Background
Individuals with adrenal insufficiency (AI) receive life-long glucocorticoid (GC) replacement therapy (CGRT), which often exceeds normal daily physiological GC production, leading to detrimental effects on cardiometabolic parameters and bone health.
Objective
Assessment of glucose, lipid and bone metabolism in AI postmenopausal patients in relation to the cause of AI and the CGRT dose.
Methods
114 AI postmenopausal women were retrospectively studied (37 primary AI [PAI] and 37 secondary AI [SAI] patients and 40 AI patients following Cushing's syndrome (CS) treatment [post-CS AI]). Biochemical glucose and lipid parameters and bone mineral density (BMD) in lumbar spine (LS) and femoral neck (FN) were evaluated at baseline and at the follow-up (2 years). Additionally, patients were divided in 3 groups based on their total daily hydrocortisone (H/C) doses (TDH/CD); low dose (LD) (TDH/CD ≤ 15 mg) (21 patients), medium dose (MD) (15 mg < TDH/CD ≤ 25 mg) (50 patients) and high dose (HD) (TDH/CD > 25 mg) (43 patients)

Results
At baseline all patients had comparable age, body mass index. duration of AI, age of menopause and. Significantly more PAI patients were on LD and more post-CS AI ones on HD. Although mean daily GC dose was equal among groups, PAI patients received significantly less GC per body surface area (BSA) ($P=0.045$). Additionally, they had P1NP levels ($P=0.013$) and lower HbA1c, TChol and LDL values compared with the other ones ($P=0.043$, 0.018 and 0.001, respectively). After 2 years' time, TDH/CD decreased among all patients. Furthermore, P1NP values remained higher and TChol and LDL values lower among the PAI patients. Regarding TDH/CD, at baseline HD patients had worse lipid profile, increased bone turnover and lower BMD and T-Score in FN and LS. At 2 years follow-up, HD patients continued to exhibit deteriorated lipid values, elevated b-cross laps and lower BMD and T-Score in LS but not in FN in comparison to the other patients.
Conclusions
PAI patients had increased bone formation and better glucose and lipid profile compared to SAI and post-CS AI patients, and this difference persisted during the two years follow-up. This possibly related to the use of lower GC doses per BSA in PAI patients. Additionally, HD therapy in AI patients exerts a longitudinal and persistent negative effect on the glucose and lipid profile and the bone metabolism. Our data enforce the need for the lowest possible GC replacement dose and the routine follow up for all AI patients.

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Retrospective study of steroid weaning in tertiary adrenal insufficiency comparing prednisolone and hydrocortisone

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Background
The hypothalamic-pituitary-adrenal (HPA) axis can be suppressed by long-term exogenous glucocorticoids, resulting in tertiary adrenal insufficiency (AI). International expert consensus suggests that during weaning, prednisolone be converted to hydrocortisone to allow HPA axis reactivation(1). There is, however, little evidence to support this practice.
Aim
To compare HPA axis recovery during treatment with prednisolone and immediate-release hydrocortisone.
Methods
This is a retrospective study of patients diagnosed with tertiary AI (failed short synacthen test [SST]) attending a dedicated adult endocrine steroid clinic between 2015-2022. Patients were either weaned down to a physiological replacement dose of prednisolone or had been converted to immediate-release hydrocortisone. Patients were followed up with repeat SST to confirm HPA axis recovery demonstrated by a subsequent normal SST.
Results
276 patients had SST of which 161 had an abnormal result. After excluding patients with no subsequent SST or taking different or multiple steroids, a total of 119 patients were included in final analysis: 41 on prednisolone and 78 on hydrocortisone (48 previously on hydrocortisone; 30 converted during study period). The rate of HPA axis recovery in prednisolone group was 61% ($n=25$), compared to 24% ($n=19$) in hydrocortisone group ($P<0.001$). There was no mean difference in age (60 v 55 years; −4.3 years, 95%CI −10.5, 1.9), sex (females 63% v 59%; $P=0.64$), baseline cortisol at 1st SST (144 v 124 nmol/l; -19.7 nmol/l 95%CI -56.5, 17.0), baseline ACTH (22 v 30 ng/ml; 7.4 ng/ml 95%CI-3.0, 18.3), or duration of underlying diagnosis (4353 v 5360 days; 1133 days 95%CI -747, 3014) between the two groups. Mean follow up duration in prednisolone group was significantly lower (354 v 579 days; 225 days 95%CI 98.6, 350.8). Recovery rate in patients ($n=30$) in prednisolone to hydrocortisone switch subgroup also had similar recovery rate (27%) to overall hydrocortisone group.
Conclusion
This is the first study to compare HPA axis recovery during treatment with prednisolone and hydrocortisone. HPA axis recovery was more common in the prednisolone-treated patients and recovery time shorter compared to those on hydrocortisone. Prospective randomised studies with standardised treatment regimens are required to confirm our findings as selection bias may have influenced the conversion to immediate-release hydrocortisone in patients predicted to have slower recovery of the HPA axis.
Reference
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Description of 38 novel ARMC5 variants and review of the literature: the updated mutational landscape of ARMC5 in Bilateral Macronodular Adrenocortical Disease

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Introduction
Bilateral Macronodular Adrenocortical Disease (BMAD) is a rare cause of Cushing syndrome due to bilateral adrenocortical macronodules. Germline inactivating variants of the tumor suppressor gene *ARMC5* have been described by our group 10 years ago and are responsible for 20-25% of apparently sporadic BMAD cases and 80% of familial presentations. *ARMC5* patients present with a more pronounced phenotype than wild-type patients, in terms of cortisol excess, number of nodules, and prevalence of Cushing's complications. *ARMC5* screening is now routinely performed for BMAD patients and families.
Methods
Based on literature review and on our own observations, this study aims to give an overview of both published and unpublished *ARMC5* genetic alterations and to compile the available evidence to discriminate pathogenic from benign variants.
Results
135 different germline variants (97 previously reported and 38 novels from our center) are identified in 212 unrelated patients, including 62 (46%) missense substitutions, 39 (29%) frameshift deletions or insertions, 24 (18%) nonsense variants, 4 (3%) affecting splice sites, 4 (3%) in-frame variants and 2 (1%) large deletions. The variants are spread on the entire coding sequence of the gene and most of them are private, with few recurrent hotspots (only 6 variants have been found in 5 or more different index patients). The pathogenic nature of *ARMC5* variants is established according to the recommendations of the American College of Medical Genetics, on the basis of their frequency in the general population, *in silico* predictions, familial segregation and tumor DNA sequencing. Indeed, in addition to the germline events, somatic 16p loss-of-heterozygosity and 70 different somatic events are described, leading to a bi-allelic inactivation of the gene, in accordance with a tumor suppressor gene model. Besides BMAD, the presence of a germline *ARMC5* variant has also been associated with the occurrence of meningiomas in 9 patients, with the demonstration of a second somatic event in 2 of them.
Conclusion
This work is the first extensive analysis of all the *ARMC5* genetic alterations reported so far in the literature with the addition of 38 unpublished variants identified in our center. A total of 196 different *ARMC5* alterations are reported here: 135 germline and 70 somatic variants (9 reported both as germline and somatic alterations). The present study is an important source of information and provides a list of variants, classified upon their pathogenic nature, which could help clinicians and geneticists to discriminate pathogenic from benign variants.

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Anxiety, depression, quality of life and sleep: new insights in adrenal insufficiency care through salivary cortisol and cortisone diurnal rhythm measurement

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Background
Adrenal insufficiency patient (AIP) care is mostly based on symptoms or clinical signs of inadequate glucocorticoid replacement treatment (GRT). Salivary

cortisol (F) and cortisone (E) recently emerged as new tools for AIP management, although poorly employed in clinical practice.
Aim
To assess associations between salivary glucocorticoid measures and life quality, anxiety depressive symptoms, sleep quality in AIP.
Method
We enrolled 29 healthy subjects (HS) and 52 AIPs under cortisone acetate (CA, $n=27$) or hydrocortisone or dual release hydrocortisone (HC, $n=25$). At observation day, subjects gathered 9 saliva samples at pre-established times from 07:00 (for AIP, immediately before the first GRT dose) to 23:00. Contextually, AIPs completed Addison disease specific quality-of-life questionnaire (AddiQoL-30; subdomains: Fatigue, Symptoms and Emotions), Hospital Anxiety and Depression Scale (HADS; subdomains: Anxiety and Depression) and Pittsburgh Sleep Quality Index (PSQI). E and F were quantified by liquid chromatography-tandem mass spectrometry. Due to GRT oral contamination, we considered F for CA and E for HC. Glucocorticoid exposure was estimated as area under the curve (AUC). F and E rhythms were determined with cosinor analysis. Z-scores (ZS) of F and E values at each time point, AUCs and cosinor parameters were calculated in the overall population including HS and AIPs. Linear and logistic multivariate regression analysis were performed including questionnaire scores as dependent variable and age, disease duration, ongoing GRT scheme duration, GRT equivalent-hydrocortisone dose, GRT type, body mass index, waist circumference and, one at a time, ZS parameters as covariates.
Results
Concerning AddiQoL, ZS-$AUC_{07:00\rightarrow07:30}$ negatively predicted Emotions ($R^2=0.125$, $P=0.040$). ZS-$AUC_{14:00\rightarrow16:00}$ negatively predicted overall score ($R^2=0.208$, $P=0.007$), Fatigue ($R^2=0.280$, $P=0.001$) and Emotions ($R^2=0.12$, $P=0.045$). ZS-$AUC_{21:00\rightarrow23:00}$ positively predicted Symptoms ($R^2=0.124$, $P=0.041$). Regarding HADS, ZS-$AUC_{14:00\rightarrow16:00}$ positively predicted the overall score ($R^2=0.338$, $P=0.004$) in model with ongoing GRT scheme duration, whereas ZS-$AUC_{19:30\rightarrow21:00}$ negatively predicted Depression ($R^2=0.136$, $P=0.045$). About PSQI, ZS-14:00 ($R^2=0.422$, $P=0.020$) and ZS-amplitude ($R^2=0.147$, $P=0.037$) positively predicted the overall score, whereas increasing ZS-$AUC_{12:30\rightarrow16:00}$ predicted abnormal PSQI (OR: 2.382; CI 95%: 1.099-5.164; overall percentage: 69%; $P=0.028$).
Conclusions
Elevated morning and, to a higher extent, afternoon glucocorticoid exposure predicted poorer life quality, stronger anxiety depressive symptoms, lower sleep quality. Interestingly, reduced evening glucocorticoid exposure predicts worse life quality and anxiety depressive symptoms, possibly indicating the need for greater glucocorticoid coverage at the end of the day. Hence, measurement of salivary cortisol and cortisone maybe useful predictors of physical and psychological wellbeing in AIP and could be employed for GRT management.

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Genetic Aetiology of Primary Adrenal Insufficiency in Sudan

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Primary adrenal insufficiency (PAI) in children is usually congenital with more than 25 causal genes leading to overlapping phenotypes. A genetic diagnosis is helpful to guide management and genetic counselling but can be challenging in resource limited settings where facilities for antibodies and genetic testing may be unavailable. Studies from Africa are rare but, in Sudan, the most common genetic aetiologies for PAI are congenital adrenal hyperplasia (CAH; mostly *CYP21A2*) and Triple A syndrome (*AAAS*). Here we describe other genetic etiologies of PAI in a cohort of 29 Sudanese families. 36 patients from 29 Sudanese families (22M) were included in this series. Inclusion criteria were clinical presentation of PAI paired with biochemical finding of low cortisol and high ACTH, and/or a negative response to synacthen stimulation. Exclusion criteria were clinical and/or genetic diagnosis of CAH or Triple A syndrome. Candidate gene sequencing (CGS) of commonly causative genes; *MC2R*, *MRAP*, *CYP11A1* and *STAR*, was followed by whole exome sequencing (WES) in mutation negative individuals and family members (where available). Qiagen Clinical Interpretation tool was used to filter variants from VCF files, and the Integrative Genomics Viewer (IGV) employed to look for small/large deletions in known causal genes. The genetic aetiology was determined in 16/29 families ($n=19$ patients). Only 1 individual was diagnosed by CGS, having *MC2R* mutation p.R146H. Other mutations were discovered in; *NNT* ($n=5$) including a novel, synonymous variant (c.2193G>A; p.T731=) causing aberrant splicing p.(Glu867_Thr731del) in three families, *ABCD1* ($n=4$), *NROB1* ($n=1$), *CYP11A1* ($n=1$), and *CYP11B1-CYP11B2* fusion ($n=3$). IGV analysis detected a deletion of the last five exons of *AIRE* in two families ($n=4$), meaning *ABCD1, AIRE* and *NNT* are the most frequently mutated genes in this population. PAI in Sudan has heterogeneous aetiology and gaining a genetic diagnosis is priceless to the patient and family, helping to guide healthcare management and provide vital information on the prognosis. Unconventional mutations in known genes or novel genes may be responsible for the remaining undiagnosed cases. CGS as a pre-screening tool may be helpful where founder effects are known, e.g. p.(T731=) mutation in *NNT* in Sudan, but WES and whole genome sequencing (WGS) are likely to become the standard to achieve this, with their ability to find single nucleotide variations and deletions respectively, especially where causative genes are already established. The challenge will then shift to proving the consequence of variants found, as seen here with the "silent" *NNT* variant.

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UK Lung cancer screening guidelines; are functional adrenal lesions being missed?

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Background
Adrenal incidentalomas are common and require investigation to exclude malignancy and evidence of hormone overproduction. Prospective screening programmes are essential for early detection of cancer but often lead to incidental findings which have potential health economic implications and may increase patient anxiety. With regards to investigation of incidental adrenal nodules, current national lung cancer screening recommendations are not in keeping with current endocrinogy guidelines regarding which nodules need further investigation. This study aimed to assess the characteristics of the patients identfied with adrenal nodules from the UK Regional Lung Cancer Screening trial.
Methods
Data were collected retrospectively on patients over a three year period. Inclusion criiteria were adult patients who had undergone a computerised-tomography scan as part of the lung cancer screening trial with an adrenal nodule >1cm incidentally identified. Demographics, imaging characterisitics (maximum axial diameter, Hounsfield Units - HU), biochemistry and outcome data were recorded.
Results
A total of 187 patients were included (55% male), mean age 69.8 years $\pm$ 7 (SD). 145 (77%) had a unilateral lesion, mean size of 2.3 ± 0.9cm. 17(9%) lesions were >4cm and 26(14%) had HU above 10. Overall 183 (98%) of the cohort underwent associated functional hormone tests, 94 (51%) had cortisol >50nmol/l on overnight dexamethasone suppression test. Of those who had plasma metanephrines, two (1%) were signifiantly elevated and 5(5%) had aldosterone:renin suggesting possible primary hyperaldosteronism (PA). Following review in the Adrenal MDT one patient was diagnosed with phaeochromocytoma and 2 with Conn's syndrome. 59 patients were diagnosed with mild autonomous cortisol secretion (MACS). Of the patients with MACS, 49 had further investigations; 13(27%) had pre-diabetes, 7(14%) had hypertension and 2(4%) had osteoporosis identified. Three patients underwent surgery. If the lung screening guidelines had been followed only 17(9%) patients would have been referred to the adrenal team and 52 of the patients with MACS would not have undergone further investigation.
Conclusions
Amongst this cohort of patients, a majority had postive functional testing requiring further review. Although this has an impact on resources, important diagnoses were made as a result, including phaeochromocytoma, PA and MACS. Additionally, further co-morbidities assoicated with MACS including pre-diabetes and hypertension were identified allowing earlier intervention. Based on these data, 91% of investigated lesions would not have warranted further evaluation if the national lung cancer referral recommendations had been followed. This analysis highlights the additional diagnoses that would have resulted from investigating all adrenal nodules greater than 1cm in diameter.

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The Relationship Between Autonomic Cortisol Secretion and Metabolic Diseases in Cases with Adrenal Incidentaloma

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Backgorund
Adrenal incidentalomas (AI) are lesions discovered incidentally on imaging without clinical symptoms or examination findings. AI can produce hormones in 5-30% of cases. Autonomic cortisol secretion (ACS) is the most common of these. Although ACS is asymptomatic, it increases the risk of metabolic disorders.
Methods
Patients aged ≥18 years with adrenal adenoma and upper abdominal MRI who presented and were examined in the endocrinology outpatient clinic, had their data retrospectively documented. Comorbidities, examinations and hormonal tests and results of these patients were evaluated. Those who failed dexamethasone suppression tests (cortisol >1.8 g/dl) and did not have Cushing's syndrome were classified as ACS.
Results
Among the 465 patients, 311 (66.9%) were women with a mean age of 54.8±10.2 (18-82). Of the patients, 31.4% had diabetes mellitus (DM), 53.8% had hypertension (HT), 30.8% had hyperlipidemia (HL), 11.8% had coronary artery disease (CAD), 1.3% had heart failure (HF) and. Hormone testing revealed that 31 (6.6%) of the patients had primary aldosteronism, 7 (1.5%) had pheochromocytoma, and 75 (16.1%) had ACS. Patients with and without ACS were compared for the presence of other additional diseases and adenoma size (Table-1). DM, HT and HL were higher in the ACS group ($P<0.05$, for each). Adenoma size was larger in the ACS group ($P<0.05$). Although the gender distribution was similar in both groups ($P>0.05$), the OCS patient was older ($P=0.006$).
Conclusion
Individuals with large adenomas are more likely to have ACS. Large adrenal adenomas should be monitored for ACS and associated cardiometabolic risks, as well as necessary treatments.

Table 1 Comparison of patient characteristics with and without autonomic cortisol secretion

Autonomic cortisol secretion	Yes $n=75$	No $n=390$	P
Sex, Woman/Man	56/19	255/135	0.11
Age (years), mean	57.8±10.8	54.2±9.9	**0.006**
Size of adenoma (mm), median (min-max)	25 (10-54)	18 (10-60)	<0.001
T2DM %	41.3	29.5	**0.04**
HT %	69.3	50.8	**0.003**
HL %	41.3	28.7	**0.03**
CAD %	18.7	10.5	**0.04**
HF %	2.7	1	0.25
Osteoporosis %	31.8	35	0.95

T2DM type 2 diabetes mellitus, HT hypertension, HL hyperlipidemia, CAD coronary artery disease, HF heart failure

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Influence of liver steatosis and fibrosis on cardiovascular function and prognosis of HFpEF patients

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Introduction
Non-alcoholic fatty liver disease (NAFLD) and Heart Failure with Preserved Ejection Fraction (HFpEF) are two syndromes with increasing clinical relevance, mainly due to the rising prevalence of metabolic syndrome. Despite sharing a common metabolic background, the association between NAFLD severity and HFpEF has not yet been well explored.
Aim
To evaluate the association of NAFLD steatosis and fibrosis scores with cardiovascular function and the risk of cardiovascular events in a cohort of individuals with stable HFpEF.
Methods
We included individuals with stable HFpEF followed in the Heart Failure (HF) Outpatient clinic at Centro Hospitalar Universitário de São João in Porto, Portugal. Patients with significant alcohol consumption were excluded. At enrolment, a comprehensive collection of clinical/imaging data and biological samples was performed. Cardiac structure and function were evaluated by echocardiography. Endothelial function and vascular properties were assessed by Reactive Hyperemia Index (RHI), measured using EndoPAT™2000 device, and pulse-wave velocity. We calculated the hepatic steatosis risk using Fatty Liver Index (FLI) and Hepatic Steatosis Index (HSI), and the liver fibrosis risk using NAFLD Fibrosis Score (NFS) and BARD score. We used linear regression models to analyze the associations between NAFLD scores and parameters of cardiac and vascular function. We performed a survival analysis to evaluate the association between NAFLD scores and the risk for a composite endpoint of urgent visits due to acute HF, HF hospitalization or cardiovascular death. Models were adjusted for age, sex, and type-B natriuretic peptides.
Results
Sixty-one patients were included. The mean age was 73.8±9.2 and 54% were female. Higher FLI and HSI levels were associated with higher posterior wall thickness [β=0.15 (0.03; 0.26); $P=0.016$; β=0.06 (0.01; 0.11); $P=0.032$, respectively]. Higher NFS index was associated with higher E/e' ratio [β=0.77 (0.00; 1.55); $P=0.049$] and E/A ratio [β=0.44 (0.01; 0.88); $P=0.044$]. Increasing BARD categories were associated with higher interventricular septum thickness [β=0.56 (0.07; 1.04); $P=0.025$] and E/e' ratio [β= 1.24 (0.36; 2.12); $P=0.007$]. A negative association was found between HSI and RHI (β=-0.04 (-0.07; -0.00); $P=0.038$). In the survival analysis, we found that higher HSI levels and higher BARD categories were associated with an increased risk for the combined outcome [HR=1.10 (1.04; 1.18); $P=0.002$; HR=2.40 (1.37; 4.20), $P=0.002$, respectively].
Conclusions
These results suggest that the presence of liver steatosis or fibrosis are associated with increased ventricular mass, impaired endothelial and diastolic functions, and with a higher risk for cardiovascular events, in individuals with stable HFpEF.

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Glucocorticoid-induced adrenal insufficiency: Identification of diagnostic and prognostic biomarkers based on two randomized controlled trials - REFINE

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Background
The risk and course of glucocorticoid-induced adrenal insufficiency (GIA) are unclear and current evidence is retrospective and based on small and selected study populations. However, the prevalence of glucocorticoid use is at least 3 %, which underscores the need for unbiased and prospective assessment of the prevalence and clinical consequences of GIA.
Objectives
To identify biomarkers of GIA as regards diagnosis, prognosis and responsiveness to hydrocortisone replacement.
Patients and Methods
The study (REFINE) is nested in two ongoing randomized controlled trials, RESCUE and REPLACE (Table 1). Both studies screen potential participants by an ACTH test with GIA defined as a stimulated 30 minute plasma cortisol concentration <420 nmol/l. We aim to prospectively screen 2.800 and enroll 555 patients in the two studies. Patients contribute blood samples at the baseline visits and after completion of the RCTs. Demographics, lifestyle factors, disease characteristics, co-morbidities, medication and patient reported outcomes (PROs) are recorded at baseline and at study end. We aim to generate diagnostic, prognostic and predictive GIA biomarkers with a stepwise analysis. First step involves univariate analyses to identify single biomarkers and generating an outline of variables for the proceeding analyses. Further analyses will proceed in two directions, prediction and explanatory associations.

Table 1 (Abstract P564)

Study	Population	Other inclusion criteria	Grouping based on ACTH-test: ACTH-stimulated cortisol at inclusion	Intervention (RCT groups)	Study length
RESCUE $n=325$	- Patients with giant cell arteritis and/or polymyalgia rheumatica	Ongoing prednisolone treatment $\geq$0 mg/day and $\leq$ 5 mg/day	RCT: <420 nmol/l ($n=250$) Control: $\geq$420 nmol/l ($n=75$)	Hydrocortisone vs placebo during stress	6 months
REPLACE $n=230$	- Age $\geq$50 years - Prednisolone treatment $\geq$12 weeks	Planned cessation of prednisolone treatment $\geq$2 weeks and $\leq$ 12 weeks ago	RCT: 100-419 nmol/l ($n=150$) Control 1: <100 nmol/l ($n=20$) Control 2: $\geq$420 nmol/l ($n=60$)	Hydrocortisone vs placebo	12 months

Selection of candidate variables for our prediction models will be based on findings in our univariate analyses and published literature and include among others a broad spectrum of clinical, biochemical, genetic as well as patient-, disease- and treatment-related variables. Our approach to establish multivariate predictions models will adhere to current guidelines.

Perspectives

This study, together with the results of RESCUE and REPLACE, will support clinical decision-making as regards predicting, diagnosing and managing GIA.

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The degree of cortisol secretion is associated with cardiometabolic complications in patients with nonfunctioning adrenal tumors

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Most adrenal incidentalomas are benign and can be divided into nonfunctioning adrenal tumors (NFAT) and tumors with mild autonomous cortisol secretion (MACS). Several studies suggest that MACS may result in an increased risk for mortality and cardiometabolic disease. The cardiometabolic risk in MACS is possibly related to the increased frequency of cardiovascular risk factors such as diabetes mellitus (DM) and hypertension (HT) induced by cortisol excess. This is confirmed by the evidence that DM and HT ameliorate after adrenalectomy in patients with MACS. Recent data suggested that not only MACS but also NFAT patients may have an increased risk of cardiovascular events (CVE). The mortality risk in NFAT seems to be comparable to that in MACS and adrenalectomy seems to be beneficial for hypertension and diabetes mellitus even in patients with NFAT. Therefore, the aim of our study was to assess: i) the association between HT, DM, obesity, dyslipidemia, and CVEs with cortisol secretion; ii) the cut-off of the cortisol secretion parameters for identifying NFAT patients with a worse cardiometabolic profile.

Patients and Methods:

In 615 NFAT patients (i.e. with 1mg overnight dexamethasone suppression test, F-1mgDST <1.8 μg/dl) F-1mgDST and adrenocorticotroph hormone (ACTH) levels and data on associated manifestations and CVE prevalence were collected.

Results

HT, DM and HT plus DM were associated with F-1mgDST levels (area-under-curve: 0.588 ± 0.023, 0.610 ± 0.028, 0.611 ± 0.033, respectively, $P<0.001$ for all comparisons) but not with ACTH. The cut-off for identifying patients with either HT or DM or HTplusDM was set at $\geq$1.2 μg/dl (33 nmol/l). As compared with patients with F-1mgDST <1.2 μg/dl ($n=289$), patients with F-1mgDST $\geq$1.2 μg/dl ($n=326$) had lower ACTH levels (17.7 ± 11.9 vs 15.3 ± 10.1 pg/ml, respectively, $P=0.008$), and higher age (62.5 ± 10.9 vs 57.5 ± 12.3 years, respectively, $P<0.001$), prevalence of HT (38.1% vs 52.5% respectively $P<0.001$), DM (13.1% vs 23.3%, respectively, $P=0.001$), HTplusDM (8.3% vs 16.9%, respectively, $P<0.002$) and CVE (7.3% vs 3.2%, respectively, $P=0.028$). F-1mgDST$\geq$1.2 μg/dl was associated with either HT (odd ratio, OR, 1.55, 95% confidence interval, 95%CI 1.08-2.23, $P=0.018$) or DM (OR 1.60, 95%CI 1.01-2.57, $P=0.045$) after adjusting for age, gender, obesity, dyslipidemia, and DM (for HT) or HT (for DM), and with the presence of HTplusDM (OR 1.96, 95%CI 1.12-3.41, $P=0.018$) after adjusting for age, gender, obesity, and dyslipidemia.

Conclusions

In NFAT patients cortisol secretion is associated with the prevalence of HT and DM; patients with F-1mgDST $\geq$1.2 μg/dl could have a worse cardiometabolic profile.

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Evaluation of CYP11B2 immunostaining findings and cure rates of primary aldosteronism subtyped by anatomical imaging and functional methods

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Background

The best lateralization method to ascertain cure after surgery in unilateral primary aldosteronism (PA) is debated. Risk of persistent of PA in those with non-classical adrenal histopathology remains poorly characterized.

Objective

We examined the value of anatomical compared with functional subtyping and the significance of immunohistochemical analysis of CYP11B1 and CYP11B2 for the outcome and histopathological diagnosis of primary aldosteronism.

Design

A retrospective multicenter study of patients operated for PA.

Methods

We identified 277 subjects with a diagnosis of primary hyperaldosteronism (E26.0) who had an adrenalectomy sample available in the Finnish biobanks during 1.1.2000-31.12.2019. Adrenal slides from biobanks were analyzed centrally after CYP11B2 staining and clinical data were obtained from patient registries.

Results

Altogether 179 (64.6%) patients underwent adrenalectomy based on anatomical lateralization on CT or MRI, whereas 43 (15.5%), 14 (5.4%) and 35 (12.6%) were operated based on functional lateralization in adrenal venous sampling (AVS); ^{11}C-metomidate (^{11}C-MTO) -PET or [^{131}I] norcholesterol scintigraphy, respectively. Adrenalectomy based on functional subtyping more likely resulted in complete or partial clinical cure than anatomical subtyping -based adrenalectomy (88.5 % vs. 72.5 %, $P=0.002$). Re-evaluation of adrenal samples with CYP11B2 staining revealed aldosterone-producing adenoma (APA) in 146 (67.3 %) subjects and changed the original histopathological diagnosis in 91 (33.2 %) of the subjects. Aldosterone-producing nodules (APN) were more frequently present in those who did not reach clinical cure (22.4 % vs 9.4 %, $P=0.012$) whereas aldosterone-producing micronodules (APM) were common overall (83.4 %) and did not impact the outcome of adrenalectomy. Frequency of APAs and non-classical features did not differ according to the subtyping method used.

Conclusions

Lateralization detected in functional subtyping can identify unilateral aldosterone production more accurately than anatomical imaging. CYP11B2 staining is elemental for the histopathological diagnosis and complements the postoperative

clinical data. Our results suggest the need for prompt long-term follow-up in patients with APNs even after removal of an APA.

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A case of bilateral adrenal haemorrhages

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Background
Adrenal haemorrhage is a rare clinical presentation with an incidence of only 5 in 1,000,000 [1]. 10% of these are bilateral adrenal haemorrhages, which has very high mortality rate of 15 % [2]
Case summary
22 years old female had C-section for persistent to breech presentation at term. She has a history of preterm delivery due to chorioamnionitis during previous pregnancy. Patient had about 1.2L post-partum haemorrhage. She deteriorated after 24 h of C-section, with hypotension pyrexia, and decreased urinary output. The blood result showed acute kidney injury (AKI), raised INR, raised procalcitonin>100ng/ml, severely deranged liver function tests, hyperkalaemia (K^+ 6.9mmol/l) and hyponatremia (Na^+ 129mmol/l). CT-abdomen showed bilateral acute adrenal haemorrhages. She was started on IV hydrocortisone along with treatment for post-partum haemorrhage, sepsis, and AKI in critical care. Following clinical improvement, hydrocortisone dose was reduced, and she had a short Synacthen test which showed subnormal response to Cosyntropin (cortisol of 207 nmol/l and 192 nmol/l) with raised ACTH of 102 ng/l. She was discharged on hydrocortisone 10/5/5 dose with outpatient endocrine follow up.
Discussion
Bilateral adrenal haemorrhages have been reported in patients with infection, trauma and anticoagulants [3]. Due to very high mortality rate, it is important to have a very high index of suspicion for treatment. IV steroids are the key if there is a suspicion of adrenal insufficiency in patients. In this case the aetiology of bilateral adrenal haemorrhage is likely multifactorial, including postpartum haemorrhage and sepsis. It is also important to distinguish in such cases whether the adrenal insufficiency is not due to central cause as postpartum haemorrhages was also noted. In this case the anterior Pituitary hormones were normal, and ACTH was raised.
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Assessment of Practice around Corticosteroid Sick Day Rules in Transplant and Oncology Services of a Tertiary Hospital in UK

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Introduction
Long term treatment with corticosteroids has been widely used, due to the well documented immunosuppressive and anti-inflammatory activity. Corticosteroids are among the most widely prescribed drugs in oncology and post-transplant patients. However, long-term treatment with a dose of corticosteroids, which equals prednisolone 5mg/day for at least 4 weeks, is very likely to result in suppressed function of the hypothalamic pituitary adrenal (HPA) axis, a condition known as tertiary adrenal insufficiency. Patients on long-term corticosteroids should be well educated on steroid sick day rules, including the risk of adrenal crisis. We aimed to assess the practice of healthcare professionals (HCP) involved in the care of transplant and oncology patients requiring treatment with corticosteroids long-term.
Method
This prospective qualitative study aimed to evaluate the educational practice of corticosteroid sick day rules among the HCP (clinician and nurses). For this purpose, we selected HCPs primarily looking after Transplant (Liver and Kidney) and Oncology patients at Royal Free Hospital NHS Trust, requiring prolonged course of corticosteroids. A survey including a set of questions was circulated among the relevant staff.
Results
Of the 30 respondents (27 physicians and 3 specialist nurses), 66% mentioned being aware of adrenal suppressive doses of corticosteroids and 70% mentioned being aware of the corticosteroid sick day rules. However, regarding corticosteroid sick day rules counselling, only 40% confirmed counselling the patients at the time of initiation of long-term corticosteroids and 27% counselled on subsequent contact after initiating treatment. Variability was observed in the content of education where 50% of HCP counselled on illness with fever, 7% counselled on treatment around major/minor surgery and Covid-19, while 27% mentioned that they do not offer specific advice on sick day rules. Regarding testing of HPA-function, majority (60%) of respondents considered testing for suspected adrenal insufficiency and would refer the patients to Endocrine Services. However, variability was observed in the timing of testing.
Discussion and Conclusion
This is the first evaluation of the education practice on corticosteroid sick day rules in oncology and transplant services of a tertiary hospital. Our results highlight the need for standardised education on sick day rule counselling along with issuing the steroid emergency card to these patients. Specific guidance and clinician training to standardise sick day rule counselling across non-endocrine specialties should be undertaken to improve the level of care of patients on long-term corticosteroids and to reduce hospital admissions with adrenal crises.

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An Analysis of Genes Involved in Vasoconstriction Causing Hypertension and Related Cardiovascular Diseases Using Whole Exome Sequencing

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Hypertension is associated with vascular changes characterized by endothelial dysfunction, increased vascular contraction, and arterial remodelling. Vascular smooth muscle (VSM) cells, which constitute bulk of vascular wall, are critically involved in these processes through their highly plastic and dynamic features and ability to undergo phenotypic differentiation. Stimulation of VSM cells by pro-hypertensive neurohumoral stimuli such as acetylcholine and norepinephrine, and vasoactive peptides like angiotensin-II and endothelin-1 induce activation of receptors coupled to phospholipase C (PLC), leading to generation of second messengers, inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3 increases intracellular Ca2+ and causes vasoconstriction. VSM contraction plays an important role in regulation of peripheral vascular resistance and blood pressure. Vascular dysfunction, excessive vasoconstriction and vasospasm could lead to major cardiovascular disorders such as hypertension and coronary artery disease. In this study, hypertensive cardiovascular patients were screened using whole exome sequencing (WES) to find possible pathogenic mutations in different genes involved in vasoconstriction. Thirteen hypertensive cardiovascular patients from three families (3 patients in 1st, 21-48 years; 5 in 2nd, 43-72 years and 5 patients in 3rd, 19-47 years of age) were selected for WES. Genomic DNA was extracted (DNA Isolation Kit, QIAamp DNA mini-Kit) at City Lab, Rawalpindi, Pakistan. DNA obtained was taken to Genome Institute of Singapore (GIS), Singapore, where final dilutions of 25µl DNA were outsourced to Proteomics Lab, Macrogen Asia Pacific, Singapore for WES. Subsequent bioinformatics analysis was performed at GIS, Singapore. We identified a novel splicing variant in SARAF gene (in two patients of family 1) involved in norepinephrine signalling pathway and a novel frameshift variant in NOX4 gene (in all patients of family 1 and 3, and two patients of family 2) involved in angiotensin-II signalling pathway. This study also found a missense variant in ADCY10 gene (in three patients each of family 2 and 3) involved in norepinephrine signalling pathway, a missense variant in TLR4 gene (in one patient of family 1 and three patients of family 2), which is upregulated by angiotensin-II and a splicing variant in GNAQ gene (in all patients of family 1 and two patients each of family 2 and 3) that encodes a protein associated with α-adrenergic receptor and angiotensin-II receptor. Variants identified in ADCY10, TLR4 and GNAQ genes were reported earlier but are extremely rare in GnomAD database. In conclusion, we report novel mutations in two genes and variants in three genes involved in vasoconstriction in hypertensive cardiovascular patients.

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P570

An Unexpected Enzyme in Vascular Smooth Muscle Cells: Angiotensin II Upregulates Cholesterol-25-Hydroxylase Gene Expression

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Angiotensin II (AngII) is a vasoactive peptide hormone and the effector of the renin-angiotensin-aldosterone system. It exerts its main physiological effects through type 1 angiotensin II receptor (AT1R), but it can also contribute to the development of cardiovascular diseases. Likewise, oxysterols such as 25-hydroxycholesterol (25-HC), the product of cholesterol-25-hydroxylase (CH25H), can have harmful effects on the vasculature since they affect vascular smooth muscle cells (VSMCs) negatively. However, there is no established connection between AngII and 25-HC production in VSMCs. Our study aimed to explore how AngII affects Ch25h gene expression in rat primary VSMCs. RNA-sequencing was used to determine which genes are differentially expressed in VSMCs stimulated with AngII compared to vehicle-stimulated cells. We performed qRT-PCR measurements to asses Ch25h mRNA levels in our VSMC samples. VSMCs were stimulated with AngII for various time spans to determine Ch25h expression changes over time. We used multiple inhibitors to specify which signaling pathways are involved in the AngII-induced Ch25h expression changes. LC-MS/MS was used to measure 25-HC levels in the supernatant of AngII-stimulated VSMCs. Our data show that Ch25h expression was robustly upregulated in response to AngII stimulus, Ch25h mRNA levels were at a peak one hour after stimulation. The AT1R, Gq/11, and p38 MAP kinase inhibitors prevented the AngII-induced Ch25h upregulation. LC-MS/MS results demonstrated that 25-HC is present in the supernatant of AngII-stimulated VSMCs. 25-HC concentration was highest (on average 8.2 ng/ml) four h after AngII stimulation. Based on our results we conclude that AngII-induced Ch25h upregulation is AT1R, Gq/11 and p38 MAP kinase signaling dependent in primary rat VSMCs. The elevation of 25-HC levels in AngII-stimulated VSMC supernatants means that CH25H enzyme is active and functional in primary rat VSMCs. Our study demonstrated that AngII stimulus induces Ch25h upregulation and subsequently 25-HC production in VSMCs. Our findings can lead to the better understanding of mechanisms in the pathogenesis of cardiovascular diseases. This work was supported by the National Research, Development and Innovation Fund (NKFI K139231 and NVKP_16-1-2016-0039).

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Calcium and Bone

P25

Expression of genes involved in parathyroid tumorigenesis identified different gene signatures in parathyroid adenomas

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The expression of key molecules involved in fundamental cell processes and epigenetic gene expression modulation is altered in human parathyroid tumours, due to gene mutations, loss of heterozygosity, aberrant gene promoter methylation, DNA copy number variations. We performed a gene profiling of 26 parathyroid tumorigenesis-related genes in a series of 32 sporadic parathyroid adenomas (PAds) surgically removed from patients with primary hyperparathyroidism, with the aim to detect specific gene signatures. Gene expression data were analyzed by unsupervised hierarchical clustering analysis using Euclidean wardd2. Clusterization was performed considering the expression of oncosuppressors (*MEN1*, *CDC73*, *RASSF1A*, *YAP1*, *CTNNB1*), embryonic transcription factors (*GCM2*, *TBX1*, *PAX1*, *GATA3*), cell cycle genes (*CCND1*, *CDKN1B*/p27, *CDKN1A*/p21, *TP73*), and long noncoding RNAs (*NEAT1*, *HAR1B*, *HOXA3AS*, *HOXA6AS*, *VLDLR-AS1*, *SNHG6*). Additionally, all PAd samples were profiled for parathyroid-related genes (*CASR*, *VDR*, *PTH*) and microRNAs (miR-372, miR-517c, miR-126-5p, miR-93-5p). Three distinct transcriptional signatures were identified: cluster 1 (C1) included 9 PAds, while clusters 2A (C2A) and 2B (C2B) included 18 and 5 PAds, respectively. Principal components analysis showed that the main driver was represented by the expression of the LncRNA *HAR1B* (PC1, 88.4% of variance), followed by *TP73* (PC2, 3.8%) and *CDKN1B*/p27 (PC3, 3.5%). PAds included in C2A had lower expression levels of the oncosuppressors *CDC73*, *RASSF1A*, *CTNNB1*, and of the transcription factors *GCM2*, *GATA3*, *TBX1*, *PAX1* than C1 PAds. Interestingly, PAds in C2A had lower levels of *CCND1* than C1 and C2B, and concomitantly lower levels of the proapoptotic *RASSF1A*-induced gene *TP73*. Moreover, *HAR1B*, *HOXA3AS*, *VLDRAS1*, *SNHG6* expression levels were lower in C2A PAds. Besides, C2A and C2B included 4 PAds overexpressing the C19MC genes miR-372 and miR-517c. However, the gene expression signature of PAds included in C2A differed from that of C2B PAds, which had higher expression of *MEN1* and *YAP1*, and of *HOXA6AS*. Interestingly, the gene signatures of PAds in C2A and C2B were associated with deeply reduced expression of *CASR* and *VDR* when compared with PAds in C1. Biochemical parameters, namely circulating ionized calcium ($[Ca^{2+}]$), total calcium and PTH were similar in patients harbouring PAds included in C2A and C1, while the gene signature of PAds in C2B was associated with higher Ca^{2+} and total calcium. No difference in age at diagnosis as well as tumour size could be detected. In conclusion, in PAds transcriptional signature of critical genes involved in parathyroid tumorigenesis was heterogeneous, suggesting the role of several pathways, which claimed to be investigated.

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P26

Long-term trajectories of bone metabolism parameters and bone mineral density (BMD) in obese patients treated with metabolic surgery: a real-world, retrospective study

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Background and Aim
Potential adverse effects of metabolic surgery on skeletal integrity remains an important concern. Bone loss is common after surgery due to multiple factors including vitamin D deficiency, altered calcium metabolism, mechanical load reduction and hormonal pattern changes. It is still not clear if the effects on bone health and calcium homeostasis vary according to each surgical technique. Further, long-term data of different surgical approaches are poor. Thus, this study aimed to describe changes in bone metabolism in subjects with severe obesity undergoing both Roux-en-Y gastric by-pass (RYGB) and sleeve gastrectomy (SG).
Methodology
A single center, retrospective, observational clinical study on real-world data was performed enrolling subjects undergoing metabolic surgery.
Results
One hundred twenty-three subjects were overall enrolled, including 31 men (25.2%) and 92 women (74.8%). RYGB procedure was performed in 67 (62.6%) and SG in 46 (37.4%) patients. The mean age at baseline was $48.2 + 7.9$ years, ranging from 28.9 to 63.4 years. The entire cohort was evaluated until 16.9 ± 8.1 months after surgery, while a small group was evaluated up to 4.5 years. All individuals were treated after surgery with calcium and vitamin D integration. Both calcium and phosphorous serum levels significantly increased after metabolic surgery and remained stable during follow up. These trends did not differ between RYGB and SG ($P = 0.245$). Ca/P ratio decreased after surgery compared to baseline ($P < 0.001$) and this decrease remained among follow up visits. While 24-h urinary calcium remained stable across all visits, 24-h urinary phosphorous showed lower levels after surgery ($P = 0.014$), also according to surgery technique. Parathyroid hormone decreased ($P < 0.001$) and both vitamin D ($P < 0.001$) and C-terminal telopeptide of type I collagen ($P = 0.001$) increased after surgery. Moreover, no significant change in osteoporosis/osteopenia rate by DXA evaluation was detected one and two years after surgery ($P = 0.109$). Despite this, significant bone mineral density (BMD) reduction was detected at femoral site after surgery ($P = 0.032$ and $P < 0.001$, respectively), also after adjustment for gender.
Conclusion
We demonstrated that calcium and phosphorous metabolism remains slightly rearranged even after several years since metabolic surgery, irrespective of calcium and vitamin D supplementation. This rearrangement is characterized by a phosphorous serum levels increase, together with a persistent bone loss, suggesting that supplementation alone may not ensure the maintenance of bone health in these patients and further therapeutic strategies are needed for longtime including lifestyle, physical exercise and bone active therapy in patients at high risk of fractures.

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P27

Evaluation of PTH deprivation effects on anxiety and stress response in a rat model of Chronic Post-Surgical Hypoparathyroidism

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Introduction
Hypoparathyroidism (HypoPT) is a rare endocrine disease which is characterized by hypocalcaemia and undetectable or inappropriately low serum parathyroid hormone (PTH). Post-surgical HypoPT (PS-HypoPT) is the most common cause, caused by accidental parathyroid removal/injury during neck surgery. From a neuropsychological standpoint, patients with PS-HypoPT present cognitive and neuropsychological symptoms: the more plausible pathophysiological mechanism resides in a direct effect of PTH in the central nervous system (CNS), since PTH Receptor 1 (PTHR1) and more abundantly PTH Receptor 2 (PTHR2) have been shown to be present in many areas of brain. However, these mechanisms are still not completely elucidated. The aim of this study was to evaluate the effects of PTH deprivation on CNS in an animal model (rat) of post-surgical hypoparathyroidism, by a cognitive/behavioural assessment approach.
Methods
A rat model (Sprague Dawley) of PS-HypoPT was obtained by the surgical removal of parathyroids at 5 weeks of age and treated with gluconate calcium 1% in drinking water to maintain normocalcemia. An experimental group of 20 PS-HypoPT rats and 20 healthy Sprague Dawley controls (WT) shamed operated, underwent biochemical testing (serum calcium) and behavioural testing namely Open Field and Elevated Plus Maze. Open Field (OF) provides information about locomotion and anxiety-related behaviours: when rats are placed into an open field, the higher is the "anxiety" level, the higher the proportion of time spent close to the wall. Elevated Plus Maze (EPM) assesses anxiety-related behaviours in rodents to explore open, unprotected spaces, compared to dark, enclosed spaces. The higher the "anxiety" levels, the lower the proportion of explorations in the open spaces in favour of the dark spaces.
Results
In OF test, the time and distance spent in the zone of interest (centre of arena) were significantly lower in the PTx group, compared with WT ($P<0.01$ and $P<0.01$). These data suggest a higher level of anxiety in PTx animals. In the EPM experiment the time spent in the close arm was significantly higher in the PTx group, compared with WT ($P<0.01$, Figure 6). This suggests a higher level of anxiety and stress in PTx group.
Conclusions
Animal model of PS-Hypo shows a higher level of anxiety and stress compared to controls. The model resembles the condition of patients with PS-Hypo. This condition could be related to the direct effect of PTH deprivation in brain in PSHypo. Further study are ongoing to highlight the molecular mechanisms.

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P28

Clinical application of vitamin D metabolites measurement using LC-MS/MS – a case of a patient with persistent hypercalcemia and two pathogenic mutations in CYP24A1 gene and parathyroid adenoma

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Introduction
24-hydroxylase, encoded by a CYP24A1 gene, is a crucial enzyme entailed in catabolism of vitamin D. Loss-of-function mutations of CYP24A1 result in hypercalcemia, not adequately concomitant high levels of 1,25(OH)2D and low PTH levels. The variety of clinical manifestations depends on age – mutations can lead to fatal infantile hypercalcemia among neonates (typically precipitated by supplementation of vitamin D), whereas adults' symptoms are usually mild. The differential diagnosis of PTH-independent hypercalcemia includes i.a. malignancy and granulomatous diseases.
Case Presentation
We report a case of a 58-year-old woman with a history of parathyroid adenoma leading to hypercalcemia, hypercalciuria and unsuppressed PTH concentration. Preoperatively, in ultrasonography, technetium-99m (99mTc) sestamibi scintigraphy, followed by biopsy, the suspected mass adjoining the upper pole of left lobe of thyroid gland was found. The patient underwent parathyroidectomy (histopathology report confirmed parathyroid adenoma), significant decrease in serum calcium was observed. Three years after the parathyroidectomy, the patient was admitted to the Department of Endocrinology because of hypercalcemia, and recurrent primary hyperparathyroidism was suspected. However, the results of biochemical tests (calcium 2.88 mmol/l (reference range 2.15-2.50 mmol/l)), PTH (intact) 7.75 pg/ml (reference range 15–65 pg/ml) and slightly elevated 1,25(OH) 2D serum concentration (90.6 pg/ml (reference range 25-86.5 pg/ml)) demonstrated PTH-independent hypercalcemia. Further investigation required the exclusion of the most common causes of PTH-independent hypercalcemia (granulomatous diseases, hypercalcemia of malignancy, vitamin D intoxication) - the results of diagnostic tests did not reveal the cause of elevated calcium concentration. Subsequently, vitamin D metabolites were measured using liquid chromatography with tandem mass spectrometry (LC/MS-MS), revealing high 25(OH)D3 (72.62 ng/ml), low 24,25(OH)2D3 (0.09 ng/ml) and elevated 25(OH) D3 / 24,25(OH)2D3 ratio (806.9 (reference range 7.0-23.6)) – suggesting the defect in vitamin D catabolism. The molecular analysis of CYP24A1 gene was conducted using Next-Generation Sequencing (NGS), two pathogenic variants were identified p.(Arg396Trp) and p.(Glu143del) (rs114368325 and rs777676129).
Conclusions
Presented case shows the importance of accurate clinical evaluation of hypercalcemia. Rarely multiple causes of hypercalcemia may coexist, which complicates the diagnostic process. In patients with PTH-independent hypercalcemia, the measurement of vitamin D metabolites using LC-MS/MS analytical technique, followed by genetic testing (e.g. NGS technology), may help to identify carriers of CYP24A1 mutations.

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P29

TransCon PTH Improves Health-Related Quality of Life and Reduces Work Limitations in Adults With Hypoparathyroidism: Patient-Reported Outcomes in the Phase 3 PaTHway Trial

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Background
Individuals with hypoparathyroidism often experience a range of symptoms associated with reduced health-related quality of life (HRQoL) and work productivity. Conventional therapy aims to alleviate hypocalcemia and acute symptoms but fails to restore normal parathyroid hormone (PTH) physiology or improve HRQoL. In the PaTHway trial, 79% of participants treated with TransCon PTH vs. 5% placebo ($P<0.0001$) met the primary efficacy endpoint (normal serum calcium and independence from conventional therapy [no active vitamin D and $\leq$ 600 mg/day of calcium]) (Khan AA *et al*, JBMR, 2022). This analysis assessed the impact of TransCon PTH on hypoparathyroidism-related symptoms, functioning, and well-being; HRQoL; and work limitations in the PaTHway trial.
Methods
PaTHway is a randomized, double-blind, placebo-controlled, 26-week phase 3 trial designed to evaluate the efficacy, safety, and tolerability of TransCon PTH. Patient-Reported Outcomes were collected at baseline and Weeks 10, 20, and 26. Descriptive statistics are reported for the Hypoparathyroidism Patient Experience Scale (HPES), 36-Item Short-Form Health Survey (SF-36), and Work Limitations Questionnaire (WLQ). Higher scores are associated with improved HRQoL (SF-36) but greater symptom frequency/impact (HPES) and more self-reported difficulties at work (WLQ).

Results
Overall, 82 participants received at least one dose of study drug, and 79 completed blinded treatment (60 TransCon PTH, 19 placebo). The TransCon PTH group had greater improvements in all mean HPES scores than placebo. With 26 weeks of TransCon PTH treatment, mean HPES-Symptom cognitive and physical domain scores improved from 39.3 and 41.4 at baseline to 18.1 and 21.6, respectively. Mean HPES-Impact daily life, psychological well-being, physical functioning, and social life and relationship domain scores ranged from 25.2-35.9 at baseline and improved to 11.4-17.3. With TransCon PTH, but not placebo, all mean SF-36 subscale scores improved from baseline to Week 26; mean physical functioning, role emotional, role physical, vitality, social function, and bodily pain scores improved into the normative range for the United States general population from Week 10 through 26. Employed participants treated with TransCon PTH had lower mean WLQ scores at Weeks 10, 20, and 26 than placebo. With TransCon PTH, mean WLQ scores improved from 32.0 at baseline to 11.3 at Week 26 for time management, 27.8 to 8.9 for mental-interpersonal demands, 31.2 to 9.9 for output tasks, and 20.4 to 9.0 for physical tasks.
Conclusions
TransCon PTH reduced hypoparathyroidism-related symptoms and self-reported difficulties at work and increased functioning and well-being. Longitudinal improvements in HRQoL were also seen with TransCon PTH treatment.

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P30

In vitro study of rapid non-genomic effects of 25(OH)D3 in preosteoblastic cells

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Background
Calcifediol ($25(OH)D_3$), the major circulating form and the direct precursor of the biologically active form of vitamin D, has been identified as an agonist ligand for vitamin D receptor (VDR) with anti-proliferative effects and gene regulatory function despite having a lower receptor affinity respect than the biologically active form of vitamin D_3. In fact, recent studies have suggested that $25(OH)D_3$ can regulate gene expression by direct binding to VDR. So, considering this, our purpose has been to investigate whether $25(OH)D_3$ could be able to activate rapid non-genomic pathways, similarly to what was observed with the biologically active form of vitamin D. In this light, we analyzed *in vitro* the Ca^{2+} intracellular following exposure to 10^{-5} M $25(OH)D_3$ in mesenchymal stem cells (MSCs) derived from human adipose tissue (hADMSCs), which had been previously described as excellent cell model systems for studying the hormonal effects of $1\alpha,25(OH)_2D_3$.
Methods
hADMSC lines were established from small subcutaneous adipose tissue biopsies. Changes in intracellular Ca^{2+} concentration on hADMSCs exposed to 10^{-5} M of $25(OH)D_3$ were determined in Fluo-4-AM loaded cells and evaluated by Laser Scanning Confocal Microscopy (LSCM). As a positive control, cells were treated with 10^{-5} M calcium ionophore A23187. Statistical analysis was carried out by ANOVA followed by Bonferroni's test with predefined experimentwise (αT) = 0.05.
Results
We showed that 4 cells, one for each cell line tested, exposed to 10^{-5} M calcium ionophore A23187 as well as 17 cells treated with 10^{-5} M $25(OH)D_3$ responded positively with a significant increase of intracellular Ca^{2+} levels. In particular, three of them reached a maximum comparable to what was achieved in cells treated with 10^{-5} M calcium ionophore A23187, whereas the other cells showed a weaker response. The average ratio of the maximum fluorescence intensity changes of the cells treated with $25(OH)D_3$ and calcium ionophore compared to the baseline fluorescence was 356% and 473%, respectively.
Conclusions and future perspective
Our data demonstrated for the first time the ability of $25(OH)D_3$ to trigger rapid non-genomic effects like other steroid hormones, such as the increase in intracellular Ca^{2+} levels in hADMSCs. Nowadays, we are profiling experiments on the same cell model to study whether calcifediol could be able also to stimulate rapid cAMP signaling pathway. These findings could lead to a greater vitamin D endocrine system understanding, paving the way for the identification of novel therapeutical targets.

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P31

Bone mineral density in children and adolescents with Cystic Fibrosis

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Background
Bone health can be affected in (young) adults with Cystic Fibrosis (CF) due to different risk factors in childhood. We aimed to analyze the prevalence of low bone mineral density (BMD) during childhood in patients with CF, its risk factors and course in time.
Methods
A longitudinal prospective cohort study was performed in children with CF aged 8-18. Anthropometric, DEXA scans and endocrine data were collected. BMD z-scores were adjusted for height. Low BMD and too low BMD scores were defined as a z-score $<$-1 and $<$-2 respectively. We analyzed if BMD was associated to body mass index standard deviation score (BMI-SDS), vitamin D status, lung function (FEV1%) and cystic fibrosis related diabetes. Patients on corticosteroids in the last 6 months were excluded.
Results
One hundred-and-two children with CF (50 boys, 52 girls) were included, with a mean age of 13.0 $\pm$ 3.23 yrs. The mean BMI z-score was -0.04 $\pm$ 1.10 and mean FEV1%-value was 85.7 $\pm$ 18.5. Mean adjusted BMD z-scores for lumbar spine (LS) and total body less head (TBLH) were 0.05 $\pm$ 1.13 and 0.14 $\pm$ 1.08 respectively, with no differences between sexes. Eighteen children (17.6%) had (too) low LS BMD, and 17 (16.7%) had (too) low TBLH BMD z-scores. In multiple linear regression analysis, TBLH-BMD z-scores were positively associated to BMI-SDS and FEV1%-values ($P=0.004$) and LS-BMD z-scores were positively associated to BMI-SDS ($P=0.007$). Forty-nine children (22 boys, 27 girls) had a second DXA-scan on average 2.15 $\pm$ 0.37 years after the 1st scan at a mean age of 14.9 $\pm$ 3.09 yrs. A significant mean decrease was seen in TBLH BMD-z score of -0.70 $\pm$ 0.76 ($P<0.001$). After multiple testing, LS BMD z-scores were positively associated to BMI-SDS ($P=0.003$).
Conclusion
Most children with CF have normal BMD, however BMD seems to decrease in time. To ensure optimal bone health, nutritional status must be monitored especially in children with decreased lung function.

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P32

Plasma Sodium Increase Is Associated With an Increase in Bone Formation in Outpatients With Chronic SIAD - A Predefined Secondary Analysis of the SANDx Trial

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Introduction
Hyponatremia is the most common electrolyte disorder encountered in clinical practice and is associated with increased mortality and morbidity, including an increased risk for osteoporosis and fragility fractures. Preclinical studies suggest osteoclast upregulation whereas a clinical study showed improved osteoblast fuction after hyponatremia normalization in hospitalized patients with SIAD.
Methods
This is a secondary analysis of a double-blind, crossover, placebo-controlled trial investigating the effect of 4-week treatment with empagliflozin 25mg/day as compared to placebo in outpatients with chronic SIAD (SANDx Trial, NCT03202667). The primary objective was to investigate the relationship between the change in bone formation index (BFI), defined as PINP/CTX, and the change in plasma sodium levels. Secondary objectives included the relationship between the change in the osteoblasts markers procollagen type 1 N (P1NP) and osteocalcin and the osteoclasts markers C-telopeptide crosslink (CTX), and the change in plasma sodium levels over the treatment periods. Linear mixed models were built with the bone markers as dependent variables, patients as random-effect and the following fixed-effects: week of treatment, serum cortisol, 25-OH vitamin D and bone marker concentration at baseline, age, gender and smoking status. Spearman correlation coefficients between bone markers and sodium levels were calculated.
Results
Six out of the 11 outpatients with a chronic SIAD were female (median [IQR] age 73 years [66, 78]). A sodium increase of 1 mmol/l was associated with an increase

of 5.21 in BFI (95%-CI: 1.41, 9.00, $P=0.013$) and with an increase of 1.48 ug/l in P1NP (95%-CI: 0.26, 2.62, $P=0.03$). Plasma sodium concentration was not associated with a change in osteocalcin ($\beta = 0.32$; 95%-CI: -0.09, 0.72, $P=0.18$), nor with a change in CTX ($\beta = 0.003$; 95%-CI: -0.008, 0.014, $P=0.324$). The effect of sodium on bone markers was independent from empagliflozin. Changes in plasma sodium were positively correlated with changes in BFI and P1NP (BFI:$\rho = 0.55$, $P<0.001$; P1NP:$\rho = 0.45$, $P=0.004$) but not with CTX and osteocalcin (CTX:$\rho = -0.21$, $P=0.184$; Osteocalcin:$\rho = 0.34$, $P=0.149$).

Conclusion

An increase in plasma sodium levels in outpatients with chronic SIAD was associated with an increase in bone formation index (P1NP/CTX), which was triggered by an increase in the osteoblast marker P1NP. This supports the importance of treating hyponatremia, particularly in older adults in whom chronic hyponatremia is also associated with falls.

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P33

Heart rate and blood pressure, but not pulse wave velocity, are higher among adults with hereditary hypophosphatemia compared to healthy controls: a cross-sectional study

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Introduction

Hereditary hypophosphatemia (HH) are rare diseases, characterized by increased levels of fibroblast growth factor 23 (FGF23), excessive renal phosphate wasting and inappropriately low 1,25-dihydroxy-vitamin D causing hypophosphatemia. In children, the diseases manifest as rickets and osteomalacia, in adults only osteomalacia. Studies in cardiovascular risk among patients with HH are few and inconclusive. Some have found left ventricular hypertrophy in children and adolescents with X-linked hypophosphatemic rickets, but not in adults with HH. Isolated conditions with increased blood levels of FGF23 are not associated with increased risk of cardiovascular disease (CVD). However, complications to conventional medical treatment with phosphate and active vitamin D such as nephrocalcinosis and hyperparathyroidism are associated with increased cardiovascular risk. Pulse-wave velocity (PWV) is a measurement of arterial stiffness being an independent predictor cardiovascular risk.

Materials and methods

We performed a cross-sectional study of 50 adults with HH and 43 age- and gender-matched controls. Heart rate (HR), blood pressure (BP) and PWV were evaluated in the morning with the participants in a fasting state using the SphygmoCor® XCEL (AtCor Medical, Sydney, Australia). According to guidelines, PWV multiplied by 0.8 is reported.

Results

Mean systolic BP was significantly higher in HH (128, 95%CI: 124-133 mmHg) vs controls (118, 95% CI: 114-121 mmHg), $P<0.001$, as was diastolic BP: HH (75, 95%CI: 72-78 mmHg) vs controls (69, 95%CI: 67-72 mmHg), $P=0.003$. HR was significantly higher in HH (64, 95%CI: 61-66 s^{-1}) vs controls (59, 95%CI: 57-61 s^{-1}), $P= 0.008$. There was no statistically significant difference between groups for PWV: HH (6.7, 95%CI: 6.2-7.1 m/s) vs controls (6.2, 95%CI: 5.7-6.7 m/s), $P=0.13$.

Conclusion

In adults with HH, we found a significantly higher HR as well as a higher systolic and diastolic BP, which is associated with an increased risk for hypertension and CVD. Although PWV was not increased, our results suggest a higher risk for the development of hypertension and thereby CVD. We suggest measurements of BP and HR as routine workups by doctors taking care of adults with HH. Further studies are needed to explore eventual risks for hypertension and CVD in HH.

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P34

Two cases of parathyromatosis in patients with recurrent primary hyperparathyroidism

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Introduction

Parathyromatosis is a rare cause of recurrent hyperparathyroidism defined as small nodules of hyperfunctioning parathyroid tissue in the soft tissues of the neck or mediastinum. The most common cause is probably the implantation of parathyroid cells into surrounding tissue during surgery and the risk of parathyromatosis increases with repeated parathyroid surgery. There is an overlap in the histologic features in parathyromatosis, atypical adenoma, and parathyroid carcinoma. Parathyromatosis still remains a difficult diagnostic a therapeutic task. We describe two cases of parathyromatosis in reccurent primary hyperparathyroidism. Both cases were negative in genetic testing for mutations in *MEN1*, *RET*, *CASR* and 14 other genes associated with hereditary parathyroid diseases.

Case Report 1

64 years old woman was referred to the third parathyroid surgery for recurrent hyperparathyroidism. Laboratory: calcium 2,8 mmol/l, PTH 12,92 pmol/l (normal range 1,3 - 7,6), normal renal function. Previous surgery: 1. parathyroidectomy of one left parathyroid gland in 2012, 2. bilateral neck exploration with removal of the left cervical thymic tissue (containing parathyroid adenoma) and the fragment tissue (supposed parathyroid adenoma) from the right side in 5/2021. The fragment tissue from the right side consisted of adipose tissue with two foci of parathyroid tissue. The third surgery represented unilateral right cervical exploration with block cervical subcutaneous tissue removal and removal of the lower right thyroid pole in 10/2022. Histopathology: nodular parathyroid tissue with smooth noninfiltrative borders, without capsules, no vascular invasion, without mitotic activity – corresponding to parathyromatosis.

Case Report 2

52 years old women was referred to the fourth parathyroid surgery for recurrent hyperparathyroidism. Laboratory: calcium 2,79 mmol/l, PTH 24,6 pmol/l (normal range 1,3 - 7,6), normal renal function. Previous surgery: 1. total thyroidectomy + left upper parathyroid removal in 2008, 2. focused left parathyroid removal in 2019, 3. parathyroidectomy of 2 adenomas (both right) and pretracheal thymic tissue removal with parathyroid adenoma and other fragment of parathyroid tissue in 1/2021. The fourth surgery represented unilateral right exploration with removal of one lower right adenoma and pretracheal adipose tissue resection in 2/2022. Histopathology: noduli of parathyroid tissue corresponding to hyperplasia or parathyromatosis.

Conclusion

Our two cases represent parathyromatosis after repeated surgery. Both of them were referred for reoperation with only mild hypercalcemia. Excesive repeated parathyroid surgery should be carefully considered. Supported by Ministry of Health Czech Republic - DRO (Institute of Endocrinology - EÚ, 00023761)

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P35

Impact of a single oral bolus of 120,000 IU of cholecalciferol on vitamin D metabolites in the elderly: the results of randomized open study

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Background

Vitamin D is a dietary micronutrient responsible for calcium and phosphorus metabolism and multiple extraskeletal actions. The assessment of vitamin D status is commonly based on measurement of 25(OH)D total concentration in serum. However, the usage of LC-MS/MS analytical technique allows to reliably assess a panel of vitamin D metabolites in serum or plasma, which may help to investigate the metabolic paths of vitamin D, especially in populations at risk of deficiency.

Methods

A randomized, two-arms, open study was conducted on 58 patients (28 female and 30 male; aged from 61 to 96 years old). The primary aim was to assess the effects of a single, high, oral dose of vitamin D_3 (120.000 IU) on serum 25(OH)D_3, 25(OH)D_2, 24,25(OH)$_2D_3$, 3-epi-25(OH)D_3 and 1,25(OH)$_2D_3$ concentrations (measured by LC-MS/MS), calculated 24,25(OH)$_2D_3$/25(OH)D_3 ratio and 25(OH)D_3/3-epi-25(OH)D_3 ratio at baseline, 3 days and 7 days after

administration, compared to control group. The secondary aim was assessment of influence of percentage of fat tissue on serum metabolites of vitamin D and their changes after bolus dose.
Results
56.6% study group attained a serum $25(OH)D_3$ concentration >30 ng/ml. All subjects, except for one patient achieved a serum $25(OH)D_3$ concentration >20 ng/ml after administration. No one exceed reference value of vitamin D (30–50 ng/ml). Among participants who received vitamin D_3 there were significant increase in $25(OH)D_3$, 3-epi-$25(OH)D_3$, $1,25(OH)_2D_3$, $24,25(OH)_2D_3$ on 3rd day after administration. $24,25(OH)_2D_3$ concentration gradually grew, achieving the highest concentration on 7th day. The percentage increase of $25(OH)D_3$ was negatively correlated with baseline $25(OH)D_3$ ($r=$-0.688, $P = 0.001$). Positive correlation between percentage increase in $25(OH)D_3$ and a percentage increase serum concentration of $24,25(OH)_2D_3$ ($r=0.954$, $P< 0.001$), 3-epi-$25(OH)D_3$ ($r=8.03$, $P<0.001$) and $1,25(OH)_2D_3$ ($r=0.789$, $P<0.001$) were found. None of the study participants developed hypercalcemia. The baseline concentration of analyzed metabolites of vitamin D in serum and their percentage increase were neither dependent on BMI nor percentage of fat tissue.
Conclusions
High dose of vitamin D rapidly increases $25(OH)D_3$ concentration in the elderly patients. The response to the bolus of vitamin D includes activation of 3-epimerase, followed by production of $24,25(OH)_2D_3$, which protects from excessive increase of active form of vitamin D.

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P36

No effects of high-dose vitamin D supplementation on white blood cell count, CRP and risk of upper respiratory tract infections in infertile men – Secondary analyses from a randomized clinical trial

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Background
vitamin D has been associated with different beneficial effects on the immune system. The vitamin D activating (CYP2R1 and CYP27B1) and inactivating (CYP24A1) enzymes, including the vitamin D receptor (VDR) are expressed in several types of white blood cells (WBC). A range of studies have explored whether vitamin D positively affects risk of and severity of respiratory tract infections such as tuberculosis, influenza, cold and COVID-19.
Objective
To determine the effect of high-dose vitamin D supplementation on WBC count, CRP and self-reported upper respiratory tract infections in infertile men.
Method
A single-center, double-blinded, randomized, placebo-controlled clinical trial (NCT01304927). Sample of 307 infertile men. The active group ($n=151$) initially received 300,000 IU cholecalciferol followed by 1400 IU + 500 mg calcium daily for 150 days, compared to the placebo group ($n=156$). The primary endpoint was to assess the effect on semen quality, which has previously been reported. The effects on WBCs (Leucocytes, neutrophile, basophile, eosinophile, lymphocytes and monocytes), CRP and self-reported symptoms of cold, influenza and fever were secondary endpoints.
Results
At baseline serum $25OHD_3$ were negatively correlated with leucocyte (* $r=$-.207; $P<0.001$), neutrophil (* $r=$-.151; $P=0.009$), eosinophil (* $r=$-.158; $P=0.007$), lymphocyte (* $r=$-.191; $P<0.001$) and monocyte (* $r=$-.160; $P=0.006$) counts. Moreover, at baseline men with vitamin D insufficiency (serum $25OHD \leq 50$ nmol/l) had significant higher eosinophile, lymphocytes and monocytes compared to men with vitamin D sufficiency (serum $25OHD > 50$ nmol/l) (0.22 x 10^9/l vs. 0.19 x 10^9/l; $P=0.038$, 2.1 x 10^9/l vs. 2.0 x 10^9/l; $P=0.046$ and 0.48 x 10^9/l vs. 0.44 x 10^9/l; $P=0.024$, respectively). After the vitamin D intervention there were no differences in WBC count, CRP or number self-reported upper respiratory tract infections (25% vs 20%, $P=0.062$) between men receiving vitamin D supplementation compared to men receiving placebo. Furthermore, a predefined subgroup analysis of men with vitamin D insufficiency (serum $25OHD \leq 50$ nmol/l), showed no difference in WBC count, CRP or self-reported respiratory infections between men receiving vitamin D supplementation compared to men receiving placebo.
*r: Pearson correlations coefficient.
Conclusions
High-dose vitamin D supplementation did not alter WBCs, CRP or risk of upper respiratory tract infections. However, serum $25OHD_3$ were negatively correlated with the majority of WBC, which indicates that 25hydroxylation of vitamin D may be linked with inflammation and WBC turnover.

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P37

Vertebral fractures in acromegaly

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Introduction
Acromegalic bone disease is characterized by an increased prevalence of fragility vertebral fractures (VFs). However, an effective, non-invasive and cost-efficient imaging technique that can diagnose early bone alterations in this category of patients is yet to found. The use of bone mineral density (BMD) is not as useful as in other causes of osteoporosis as excess GH leads to specific microarchitectural alteration of trabecular bone, which don't translate to an important decrease in BMD. Trabecular bone score (TBS) is a more novel technique proposed for use in these patients.
Methods
We performed a cross-sectional study on 71 acromegalic patients, with either controlled, cured or uncontrolled disease. The turnover markers evaluated for both groups were alkaline phosphatase, osteocalcin, the C-terminal telopeptide of type I collagen and total procollagen type 1 amino-terminal propeptide (P1NP) and the imaging techniques performed were dual x-ray absorptiometry to evaluate BMD, T and Z scores of the lumbar spine (LS), femoral neck (FN) and total hip (TH), TBS and x-ray scans of the thoracic and lumbar spine.
Results
The patients had a prevalence of moderate of severe VFs of 29.6%, mild fractured not having been taken into consideration. Acromegaly subjects with and without hypogonadism had no significant differences in terms of BMD (LS: 1.07 ± 0.176 vs. 1.129 ± 0.23 g/cm2, $P=0.229$, FN: 0.999 ± 0.151 vs. 0.954 ± 0.124 g/cm2, $P=0.198$, TH: 1.03 ± 0.148 vs. 0.996 ± 0.148 g/cm2, $P=0.349$), TBS (1.182 ± 0.148 vs. 1.141 ± 0.183, $P=0.308$), or VFs prevalence (31.81% vs. 25.92%, $P=0.597$). Acromegaly patients with VFs had significantly lower osteocalcin and P1NP levels than those without VFs, as well as lower BMD at all skeletal sites (LS: 1.015 ± 0.18 vs. 1.124 ± 0.199 g/cm2, $P=0.034$; FN: 0.904 ± 0.117 vs. 1.015 ± 0.14 g/cm2, $P=0.002$; TH: 0.933 ± 0.13 vs. 1.052 ± 0.141 g/cm2, $P=0.001$). Nonetheless, TBS did not present significant differences in fractured compared to non-fractured patients (1.131 ± 0.171 vs. 1.181 ± 0.158, $P=0.238$). Furthermore, males and females with acromegaly did not have statistically significant differences in BMD, TBS of VFs frequency. Also, disease activity did not influence BMD, TBS or VFs prevalence.
Conclusions
According to our results, vertebral fractures are frequent in acromegaly, with a prevalence of around 30%, and are associated with lower BMD but not with TBS. Moreover, the presence of hypogonadism does not influence BMD, TBS or VFs prevalence in these patients and neither do gender or disease activity.

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P38

Association of Dietary Intakes of Calcium/Phosphorous with Biochemical Osteomalacia and its Components

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Background
Our previous study revealed a high prevalence of abnormal mineralization markers namely low 25 hydroxyvitamin D (47.9%); high serum alkaline phosphatase (3.7%) and low calcium-phosphate product (9.8%) suggestive of biochemical signs of osteomalacia (OM, defined as any two of these risk factors). OM was more prevalent in girls (11.2%) compared to boys (5.0%). In this follow-up study, we aimed to evaluate if biochemical OM was associated with low intakes of calcium and phosphorous.
Methods
Saudi adolescents ($n=2938$, 57.8% girls), aged 12-17 years from 60 different secondary and preparatory year schools in Riyadh, Saudi Arabia were included in this study. A dietary recall for daily intakes of nutrients/minerals using a validated computerized food database "ESHA—the Food Processor Nutrition Analysis program" was collected. Compliance to reference daily intake (RDI) was calculated. Fasting blood samples were collected and circulating levels of 25 hydroxyvitamin D, alkaline phosphatase, calcium, phosphate, and C-terminal telopeptide (CTX) were analyzed.
Results
A total of 1703 Saudi adolescents (991 girls, 712 boys) provided the dietary recall data. A major proportion (89.6%, 92.2%) of the participants failed to achieve the RDI of 1000 mg/day and 10 mg/day of dietary calcium and vitamin D respectively. The average daily dietary calcium intake was significantly lower in girls compared to boys (median levels of 294.3 and 345.5 mg/day respectively, $P<0.001$). In contrast, boys reported lower dietary intakes of phosphorous compared to girls ($P<0.01$). Interestingly, no significant correlation in status of biochemical OM or its individual risk factors with dietary calcium intake was found, irrespective of sex. However, circulating 25 hydroxyvitamin D and alkaline phosphatase levels correlated negatively with daily dietary intakes of phosphorous in girls ($r=-0.18$, $P<0.001$) and boys ($r=-0.14$, $P<0.05$) respectively.
Conclusions
This study suggests a need for vitamin D fortification and increased dietary calcium in the diet of Saudi adolescents. The results also show that all adolescents exceeded the RDI for dietary phosphorous but none met the RDI for dietary calcium and vitamin D, and none had sufficient 25 hydroxyvitamin D levels (>50nmol/l). We speculate that the high phosphate diet may somehow compensate for the insufficient supply with calcium and vitamin D. This insufficient supply would otherwise have caused a much higher prevalence of biochemical OM than the 6.2% we observed.

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P39

4D-CT parathyroid increases the likelihood of localising parathyroid adenoma (PA) in patients with primary hyperparathyroidism (PHPT) and non-diagnostic Tc99m-Sestamibi + I-123 subtraction scan

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Introduction
Tc99m-Sestamibi + I-123 subtraction using planar and SPECT-CT (SPECT-CT ^{99m}Tc-MIBI parathyroid) is commonly used to investigate primary hyperparathyroidism (PHPT). We previously reported the sensitivity and positive predictive value of 4D CT parathyroid as the second line investigation in patients with non-diagnostic SPECT-CT ^{99m}Tc-MIBI parathyroid (https://www.endocrine-abstracts.org/ea/0041/ea0041ep164). A common cause of indeterminate SPECT-CT ^{99m}Tc-MIBI parathyroid is the confounding factor of multi-nodular goitre or nodules. We have continued to use this investigative modality regarding pre-operative parathyroid adenoma (PA) localisation and informed patients the chance of finding parathyroid lesion in question at surgery. Patients with positive SPECT-CT ^{99m}Tc-MIBI parathyroid were referred without 4D CT parathyroid for surgery as appropriate.
Description of methods/design
We have retrospectively reviewed and analysed our case series of patients with surgically proven PA who had also 4D-CT parathyroid following non-diagnostic ^{99m}Tc-MIBI parathyroid. Demographic data (age, sex, pre and postoperative calcium/PTH) were presented as descriptive statistics. Histopathology report of surgical specimens was also verified. Sensitivity and specificity of 4D-CT was calculated with surgically proven PA as the reference standard.
Results
A total of 13 patients had non-diagnostic ^{99m}Tc-MIBI parathyroid for PHPT; 10 had positive 4D-CT parathyroid (9 confirmed PA or hyperplasia, 1 normal parathyroid tissue following surgery). 3 had normal 4D-CT parathyroid (2 confirmed PA and 1 histology showed normal parathyroid tissue). In patients with surgically proven PA, 4D-CT parathyroid performed pre-operatively demonstrated a sensitivity of 82% and a positive predictive value of 90%.
Conclusion
In our case series of patients with non-diagnostic ^{99m}Tc-MIBI parathyroid for investigation of PHPT, 4D-CT parathyroid demonstrated a consistent diagnostic value for pre-operative evaluation. Although the number of cases is small, which may limit the power of this study, it remains the preferred second line investigation of choice with high sensitivity and predictive value that allows accurate PA localisation for parathyroid surgery. With this imaging modality, both patients and the operating surgeon can be better informed of the high likelihood of finding of PA prior to surgery.

Keywords
Hyperparathyroidism, 4D-CT parathyroid, calcium metabolism.
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P40

Polymorphisms in genes related to iron metabolism and DNA methylation and their interaction with estradiol in susceptibility to osteoporosis in postmenopausal women

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Introduction
Osteoporosis is a multifactorial disease characterized by reduced bone mass and increased risk of fragility fractures. Menopause predisposes women to osteoporosis due to declining estrogen levels. Iron is known to play a relevant role in the development of osteoporosis since iron suppresses osteoblast formation and may also stimulate osteoclast resorption of bone. Also, homocysteine is a known risk factor for osteoporotic fractures and is related to DNA methylation, suggesting that polymorphisms in genes affecting both can increase susceptibility to the development of osteoporosis.
Objectives
This study aimed to investigate the potential implication of genetic polymorphisms in genes related to iron metabolism and DNA methylation and their interaction with estradiol in the development of osteoporosis in a sample of postmenopausal women.
Material and methods
A case-control study was carried out for a sample of 305 Portuguese postmenopausal women, of which 156 had osteoporosis and 149 had normal bone mass. Polymorphic analyses on the *HFE* (H63D and C282Y) and *MTHFR* (C677T) genes were performed by PCR-RFLP. The *Hp* phenotype was determined by polyacrylamide gel electrophoresis. Plasma 17β-estradiol concentration was determined by ELISA. The results were adjusted for age and body mass index. All statistical analyzes were performed using SPSS software, version 24.0.
Results
An association was found between 17β-estradiol and osteoporosis, being a protective effect observed in the presence of higher levels of estradiol [OR (95% CI) = 0.456 (0.215-0.968); $P=0.041$]. Significant differences were found for the *MTHFR* gene, with the TT genotype being protective for osteoporosis [OR (95% CI) = 0.283 (0.097-0.823); $P=0.021$]. Also, women who had the *Hp* 1 allele and higher levels of estradiol had increased protection for osteoporosis [OR (95% CI) = 0.270 (0.081-0.859); $P=0.032$], as well as in the presence of the T allele of the C677T polymorphism and higher levels of estradiol [OR (95% CI) = 0.100 (0.026-0.375); $P=0.001$].
Conclusion
Since these genes are related to iron metabolism and DNA methylation, the results of this study suggest their participation in interaction with estradiol for the development of osteoporosis in postmenopausal women.

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P41

Vitamin D status and biomarkers of bone health in diabetic adolescents and children in a multi-ethnic cohort

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Objectives
This prospective study aimed at investigating (1) the prevalence of vitamin D deficiency and insufficiency in diabetic adolescents and children in a multi-ethnic cohort, and (2) any association between vitamin D status and ethnic background, glycaemic control (HbA1C), biomarkers of metabolic bone health and lipids.
Methodology
Venous blood was drawn from 199 patients with type 1 diabetes (mean age ± SD, 8.2 ± 3.7 years) and 48 patients with type 2 diabetes (mean age ± SD, 12.7 ± 2.7 years) during their outpatient appointments in a tertiary hospital. Vitamin D status was classified according to serum 25-hydroxyvitamin D (25OHD) concentrations as deficient (less than 12 ng/ml), insufficient (12-20 ng/ml) or sufficient (more than 20 ng/ml) (Munns *et al*, 2016). Concentrations of biomarkers were measured on Abbott Alinity (calcium, magnesium, phosphate, alkaline phosphatase, HbA1C, total cholesterol, LDL-cholesterol and HDL-cholesterol) and Beckman Access II [25OHD and parathyroid hormone (PTH)] automated analysers.
Results
Vitamin D insufficiency (25OHD from 12 to 20 ng/ml) was highly prevalent in both type 1 (42%) and type 2 (50%) diabetes patients, whereas vitamin D deficiency (25OHD <12 ng/ml) was detected in 11% of type 1 and 15% of type 2 diabetes patients respectively. Deficiency or insufficiency of vitamin D was particularly common in the Indian and Malay ethnic groups. Patients of Indian extraction had the lowest mean (± SD) serum 25OHD among all four ethnic groups: 16.1 (± 5.6) ng/ml and 14.1 (± 3.8) ng/ml in type 1 and type 2 diabetes patients respectively. Among type 1 patients, Malays had lower 25OHD than the Chinese ($P<0.01$) and Others ($P<0.05$) ethnic groups. Vitamin D deficiency was found to be associated with lower calcium ($P<0.001$) and higher PTH ($P<0.001$) concentrations compared with the sufficiency group (25OHD >20 ng/ml) in type 1 diabetes patients but not in type 2 patients. Concentrations of magnesium, phosphate, alkaline phosphatase, HbA1C, total cholesterol, HDL-cholesterol and LDL-cholesterol were not associated with 25OHD in either of the two types of diabetes patients.
Conclusions
Statistically significant differences in 25OHD concentrations were detected among the four ethnic groups. Ethnicity is a risk factor for vitamin D deficiency in both types of diabetes. Vitamin D deficiency was also associated with biomarkers of poorer metabolic bone health (lower calcium and higher PTH) in type 1 diabetes patients.
Reference
Munns *et al*. (2016) *Hormone Research in Paediatrics* 85:83–106.
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P42

A single center experience with opportunistic diagnosis of osteoporosis by artificial intelligence-the time has come
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Background
Osteoporosis (OP) is underdiagnosed and frequently left untreated. CT derived bone mineral density (BMD) and identification of vertebral compression fracture (VCF) on CT done for another indication are 2 new artificial intelligence (AI) based techniques for opportunistic diagnosis of OP. Our aim was to assess the clinical impact of opportunistic diagnosis of OP
Methods
This retrospective study included men and women over age 50, insured by Clalit HMO, who underwent a CT scan for any reason at our institution and were identified by NanoxAI software as having a VCF in one or more vertebrae. Patients were excluded if a radiologist did not confirm the VCF, had a prior diagnosis of a motor vehicle accident (MVA), multiple myeloma, or spinal metastases. CT-derived BMD was calculated using Hounsfield units (HU) and when available results of DXA-BMD were retrieved. Demographic, clinical, and biochemical data including medication purchase were collected from the electronic medical records.
Results
In a 4 months period, one hundred and fifty-one patients with VCF met the inclusion and exclusion criteria, of which only 71 (47%) had a prior diagnosis of osteoporosis. Of the 71 patients with prior diagnosis of OP only 12.7% purchased any OP medication in the 2 years prior to the index CT. Patients without a prior diagnosis of osteoporosis were younger (mean age 73.02 vs. 77.27; $P=0.016$) and had higher rates of male gender (58.8 vs. 26.8%; $P<0.001$). Ethnicity and marital status were similar in both groups as were rates of prior diagnosis of diabetes mellitus and rheumatoid arthritis. Twenty-five-dihydroxy vitamin D levels were higher and alkaline. phosphate levels were lower in patients with a prior diagnosis of OP (69.25 vs. 53.29 nmol/l; $P=0.038$), and (101 vs. 78 U/l; $P=0.025$) respectively. Only 28% of the cohort underwent BMD-DXA scans in the 4 years prior to the index CT; T scores were significantly lower in the group with prior diagnosis of OP in spine (-0.29 vs. -2.22; $P<0.001$), femur neck (-1.66 vs. -2.42; $P=0.009$) and total hip (-1.18 vs. -2.3; $P=0.004$). while CT derived BMD equivalents were similarly low in both groups with VCF irrespective of prior diagnosis of OP (95.05 vs. 90.33 HU $P=0.540$).
Conclusion
Our results highlight the underdiagnosis and the treatment gap in osteoporosis which was significantly higher in men. Routine opportunistic diagnosis of OP by AI is feasible and will contribute to improved diagnosis and treatment of OP.
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P43

Primary hyperparathyroidism in an adolescent presenting with genu valgus progressing to extensive bone disease; a case report
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Background
Primary hyperparathyroidism which is rare in adolescents presents commonly with non-specific symptoms and systemic complaints. Though there are few reported cases of genu valgus, progression to extensive bone disease with fractures has not been commonly reported. Additionally, hypercalcaemia at the time of presentation was almost universal.
Case presentation
A 12-year-old male had been evaluated for bilateral (left > right) genu valgus and short stature. Serum calcium and phosphate levels had been normal. X-ray of the femora and pelvic bones had not shown additional abnormalities. Valgus deformity progressed despite left femoral plating, and a left distal femoral medial closed wedge osteotomy had been performed at 15 years. Plain imaging at that time had shown localised osteopaenia. At the age of 17 years, he developed multiple fragility fractures of his left hip rendering him wheelchair-bound. Further evaluation revealed a serum PTH level of 2571 (10-65) pg/ml with calcium of 2.82 (2.2-2.6) mmol/l and inorganic phosphate of 1.7 (2.2-4.7) mg/dl. The alkaline phosphatase level was 4785 IU/l and the vitamin D level was 24.96 ng/ml. The lumbar spine DXA scan showed a Z-score of -5.8. Diffusely scattered lytic bone lesions with associated bone expansion suggestive of brown tumours of hyperparathyroid bone disease were noted in the CT scan of humeri. There were no features of rickets. A left parathyroid adenoma measuring 51×30x16 mm was localised. He underwent left parathyroidectomy and left thyroid lobectomy after which his PTH level dropped to 4.03 pg/ml. Histology confirmed a benign parathyroid adenoma. He developed hypocalcaemia which was managed successfully with calcium and alfacalcidol replacement. Three months after the surgery, his alkaline phosphatase level dropped to 380 IU/l.
Conclusions
Cases of adolescents presenting with genu valgus due to primary hyperparathyroidism have been reported before. However, fractures and severe bone disease are exceedingly rare. Initial normocalcaemia, probably related to concomitant vitamin D deficiency could have masked the diagnosis leading to delayed diagnosis and extensive irreversible bone disease. High-index of suspicion and close surveillance is warranted in atypical presentations to avoid a delayed diagnosis of underlying metabolic disease.
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P44

CYP24A1 mutation - a rare cause of hypercalcemia and nephrocalcinosis in adulthood
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Background
CYP24A1 gene encodes the enzyme vitamin D 24-hydroxylase, which converts active vitamin D to inactive metabolites. More than 20 currently described, usually biallelic pathogenic variants of this gene are responsible for idiopathic infantile hypercalcemia manifested typically in childhood (often in newborns)

with hypercalcemia, hypercalciuria and nephrocalcinosis. However, a few patients (mostly with monoallelic heterozygous pathogenic variant) can develop mild symptoms – typically intermittent hypercalcemia dependant on vitamin D exposure together with hypercalciuria and nephrocalcinosis - in adulthood.
Case description
We present the case of 43-year old male patient with hypertension and heterozygous Leiden mutation who was sent to endocrinological examination due to hypoparathyroidism, fluctuating hypercalcemia, hypercalciuria and CKDG2A1 caused probably by nephrocalcinosis. Complete laboratory and imaging methods (parameters of calcium-phosphate metabolism, bone scintigraphy and PET-CT) excluded PTH-related peptide-mediated hypercalcemia and granulomatosis. Genetic analysis of gene encoding calcium-sensing receptor did not show any pathogenic variants. Finally, the genetic analysis of CYP24A1 gene revealed the presence of a novel combination of two heterozygous pathogenic variants: CYP24A1: c. 443T>C p.(Leu148Pro) and c.1186C>T p.(Arg396Trp). Unfortunately, the segregation analysis of the proband's parents in order to confirm trans-heterozygosity (as considered) of the pathogenic variants was not performed due to unwillingness of his parents to undergo the testing.
Conclusion
Differential diagnosis of patients with hypercalciuria, nephrocalcinosis and hypercalcemia related to vitamin D exposure should include CYP24A1 gene mutation. To our knowledge, we were the first to describe this novel combination of two heterozygous pathogenic variants of CYP24A1.

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P45

Incidence and clinical correlates of persistent hyperparathyroidism among kidney transplant patients at a tertiary specialty center

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Background
Secondary hyperparathyroidism (HPT) is a common complication seen in 12-54% of end stage renal disease patients (ESRD), owing to the calcium and phosphorus perturbations in these patients[1]. Successful kidney transplantation (KT) is expected to correct these abnormalities, however, it is not uncommon for hyperparathyroidism to persists post-transplantation [2,4,5,22]. Persistent hyperparathyroidism is associated with significant mortality and morbidity but remains to be underdiagnosed [3,22,23,34]. Local data on the incidence and associated risk factors is still scarce.
Objectives
The aim of this study was to identify the incidence of persistent hyperparathyroidism among kidney transplant recipients. Also, the risk factors for persistent hyperparathyroidism among kidney transplant patients and the effects of kidney transplantation on parathyroid hormone, calcium and phosphorus were identified.
Methods
This is a single center observational cohort study with retrospective chart review. A total of 38 kidney transplant recipients with from July 2017 to September 2019 were included.
Results
The incidence of persistent hyperparathyroidism after kidney transplantation was 60.5%. Kidney transplant recipients had a decrease in intact parathyroid hormone (iPTH) levels by 77.74%. The absolute change was similar between those with vs without persistent hyperparathyroidism. Moreover, serum phosphorus significantly decreased post-transplantation. Patients with pre-kidney transplantation intact parathyroid hormone $>$ 400 pg/ml, pre-kidney transplantation alkaline phosphatase $>$ 290 IU/l, and chronic glomerulonephritis as an etiology of end stage renal disease were identified as risk factors.
Conclusion
Several risk factors for persistent hyperparathyroidism development were identified. High risk patients must be evaluated for parathyroid enlargement and evaluated closely pre- and post-kidney transplantation.

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P46

Cardiovascular aspects of primary hyperparathyroidism

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Introduction
Primary hyperparathyroidism (PHPT) is typically characterized by elevated serum calcium associated with elevated or non-suppressed levels of parathyroid hormone (PTH). These biochemical features are both known to affect the cardiovascular (CV) system. There is a conflicting debate regarding the CV manifestations of PHPT. the aim of our study is to evaluate the cardiovascular profile in patients with PHPT.
Methods
We conducted a retrospective descriptive study at the military hospital of Tunis including 32 patients hospitalized for the management of PHPT. Clinical and paraclinical data were collected from medical records.
Results
Our population consisted of 13 men and 19 women with a mean age of 59,4 $\pm$ 13 years old. Hypertension, type 2 diabetes and dyslipidemia were found in respectively 31%, 21% and 6% of cases. Our patients were smokers in 12% of cases. Two patients had a medical history of a stroke and none of the patients had coronaropathy. Sixty-two percent of our patients were overweight and only one patient was obese with a mean body mass index equal to 25,6 $\pm$ 3,6 Kg/m^2. The mean blood pressure was 140/80 mmHg. The mean heart rate was 82 $\pm$ 19 bpm. The electrocardiogram was pathological in 25% of the cases, revealing shortening in the QT interval. All patients had echocardiography. It was pathological in six patients having shown hypertensive cardiopathy in four patients, left ventricular hypertrophy in five patients associated with mitral insufficiency in one patient, and an ischemic heart failure in one patient.
Conclusion
Based on the current evidence, cardiovascular disease is not included among the criteria needed for parathyroidectomy. Thus, long-term longitudinal randomized trials are needed to determine the impact of surgery on cardiovascular diseases and mortality in PHPT.

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P47

Case Studies of Pet Colina for Hyperparathyroidism Diagosis

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Introduction
The diagnosis of hyperparathyroidism can be challenging especially when surgery is mandatory and imaging techniques can not find the adenoma. PEt colina is a non-invasive diagnostic test that creates images of the parathyroid glands and detects abnormal activity. It is increasingly used and especially useful when there are no pathological findings in parathyroid scintigraphy.
Methods
This is a retrospective observational study with data from 10 patients with diagnosis of hyperparathyroidism and no pathological findings in scintigraphy
Results
All the patients had been diagnosed with hyperparathyroidism and had normal parathyroid scintigraphy. The medium PTH level was 174 pg/ ml (48,7) and the medium calcium level was 11,08 mg/ dl (0,87). A parathyroid scintigraphy was performed to all of them without pathological findings. Afterwards they went under a PET colina. The results showed an hyperfunctioning adenoma in 8 of them. After a parathyroidectomy all of them were cured. In 2 patients there were no findings.
Conclusion
Although scintigraphy remains the gold standard for the diagnosis of parathyroid adenomas there are a significant number of patients which show no results. Under these circumstances PET colina has proved to be an useful test.
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P48

Primary hyperparathyroidism related to ectopic thymic parathyroid tissue: about two cases

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Introduction
Primary hyperparathyroidism (PHPT) is a common endocrine disorder most commonly caused by a single adenoma of the parathyroid gland and rarely related to ectopic thymic parathyroid adenoma.
Observation
1st case: we report a case of a 46-year-old woman, diagnosed with PHPT. Scintigraphy concluded to a left inferior parathyroid adenoma. She underwent a focal parathyroid surgery and the adenoma was located in the thymus. The histopathology had shown an hyperplasic parathyroid tissue within a thymic parenchyma. Soon after surgery, persistent hypercalcemia up to 3mmol/l with elevated PTH level were noted. A skeletal survey showed generalized decrease in bone density. The neck ultrasonography was unremarkable as well as CT neck scan. Parathyroid scintigraphy showed a probable right inferior parathyroid adenoma. The patient was discharged with plans of a secondary surgical revision.
2nd case: Our case is of a 66-year-old woman operated for multinodular goiter: total thyroidectomy with left parathyroidectomy of a 7 mm adenoma that was found during surgery. Two years later, hypercalcemia(3 mmol/l) hypophosphatemia(0.6mmol/l)and overtly elevated PTH level, all contributed to the diagnosis of PHPT. Scintigraphy showed a mediastinal ectopic parathyroid adenoma, cervicothoracic CT scan showed an ectopic parathyroid adenoma of 13.7 mm in the left thymic cavity. The diagnosis of a persistent PHPT related to a mediastinal ectopic parathyroid adenoma was adopted. The patient underwent, a left thymectomy surgery. Her PTH and serum calcium levels decreased significantly. No new lesions could be detected on any of the follow-up visits.
Discussion
Parathyroid glands and the thymus share a common embryological origin which could explain the presence of ectopic thymic parathyroid.

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P49

Pregnancy and Lactation Associated Osteoporosis -A Rare Case Report

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Context
Pregnancy and lactation -associated osteoporosis (PLO) is an uncommon condition affecting women during late pregnancy and the early postpartum period. PLO is manifested with fractures usually in spine or occasionally in the hip with severe and prolonged pain and height loss. Pathogenesis of this rare condition is still not completely understood.
Case Presentation
We report a 28 y/o female patient presenting with severe back pain during postpartum period. Vertebral and Lumbar MRI revealed Th11, Th12, L1, L2 and L4 compressive fractures while DEXA scan reported severe osteoporosis - L1-L4 Z-score = -5.1 with maximal reduction of BMD in L4 -Z score - 5.6. Secondary causes of osteoporosis such as: celiac disease, Cushing Syndrome, hyperparathyroidism and hyperthyroidism were excluded. Patient was prescribed Calcium, Vitamin D, denosumab 60 mg SC every 6 months and lifestyle modification. She was consulted about the risks of severe osteoporosis, as well as possible teratogenic effects of the antiosteoporotic medication and proper contraception was advised. On repeated DEXA scan after 1 year showed improvement in bone density. After 18 months of PLO diagnosis unplanned pregnancy was confirmed. Regarding the challenges of maternal and fetal health the group discussion with Endocrinologist and Gynecologist was conducted. Patient was informed about the risks of further fractures during pregnancy and postpartum, risks of discontinuation and subsequently withdrawal of denosumab, as well as possible teratogenic effects of osteoporosis treatment. After careful judgment patient decided to terminate pregnancy and continue osteoporosis treatment with Calcium, Vitamin D and bisphoshonates.
Conclusion
We should bear in mind the possibility of pregnancy and lactation -associated osteoporosis in women with persistent back pain during pregnancy or postpartum period. Early diagnosis, proper management and patient education is crucial for maternal as well as for fetal health. Lack of data regarding antiosteoporotic treatment during pregnancy is a challenge for patients and the care takers. Further research and more evidence is needed for further guidance.

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P50

Impact of the Covid19 pandemic on patients with primary hyperparathyroidism

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Introduction
The development of the Covid-19 pandemic infection, which started in March 2020 in Tunisia, has impacted all medical specialties. Endocrine care professionals were part of this battle, as many patients with endocrine diseases including primary hyperparathyroidism (PHPT) were also affected by the pandemic. the aim of our study was to evaluate the Impact of the Covid19 pandemic on patients with PHPT.
Methods
This is a retrospective descriptive study of 28 patients diagnosed with PHPT and hospitalized between January 2018 and December 2021 at the endocrinology department of the military hospital of Tunisia. Clinical and paraclinical data were collected from medical records.
Results
Our population consisted of 10 men and 18 women with a mean age of 61.14 ± 12.16 years. The mean calcemia was 3 ± 0.4 mmol/l. The mean PTH was equal to 318 ± 337 pg/ml. COVID-19 infection was noted in 69.1% of our patients. Sixty-eight per cent of them required hospitalization. Irregular follow-up during the covid pandemic was noticed in 64% of our patients and 57% were lost to follow-up. only eight patients (29.6%) underwent surgery during this period and the surgery was delayed for the other patients. Among those who did not undergo surgery, four patients developed renal lithiasis during this period and five patients had a decrease in bone density.
Conclusion
The management of PHPT during the COVID-19 pandemic, when surgery is not possible and hospital visits are limited, presented a challenging clinical situation. Appropriate distant follow-up and monitoring of these patients was essential until the resolution of the pandemic.

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P51

Osteoporosis issues & Complementary Medicine: Three years Experiences in Asian population

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Issues
No specific centre in asia for Osteoporosis patients treatment/rehabilitation. We used locally available Complementary Indian Medicines [CAM] for providing home based care in rural/tribal areas.
Aims
To provide CAM to poor patients in collaboration with Traditional-faith-hearers. Evaluated cost-efficacy of CAM & response of pain of fractures to CAM alongside analgesics.
Methods
from April 2014 to November 2018, 122 patients [n = 122] of RA aged 34-67 years enrolled. 68% females, 32% males. 43% returned to villages after prolonged therapy in city hospitals on allopathic drugs. 12% physical deformities. self report questionnaire distributed to patients attending NGO clinics Our NGO nurses treated patients with TFH in providing CAM. Mud therapy 21%, Bach-flower remedy 40%, Accupressure/Accupuncture 57%, Hydrotherapy 24%, Hypnotherapy 75%, ayurvedic therapy 82%, 26% on Unani Medicines, 61% on Homeopathic medicines, 72% on Herbal-Oil-TFH massage therapy, 58% Aromatherapy.
Results
We treated patients in 16 sessions CAM. feedback Performa given to subjects & responses evaluated periodically to modify treatment methodology. Our NGO module in functioning stages shown graphically to IOF-2010 conference participants. Average pain recorded weekly on a scale of 1 to 10. mean score pain fell from 8.2 (SD 1.4) to 3.8 (SD 2.7) points, which is highly significant ($P < 0.001$). Symptom relief($n = 90$), Gr-1 wanting to find alternatives to drugs($n = 95$). Cost of CAM 52% cheaper compared to Allopathic medicines & islocally & has high acceptance
Conclusion
122 of patients used & preferred CAMs. Cost wise cheaper & patient compliance better. 12 % dropped out of sheer frustration/fatigue. Patients need Psychosocial-Rx, Palliative-care-centers. Realizing divergent versions of CAM, multicentre study on this burning issue must be carried out. At ECE-2023 We shall form group with researchers from USA/Europe to substantially improve CAM approach. We NGO-representatives from developing nations need exposure to research technicalities/-methodologies used by European/American experts in management of osteoporosis. This is indeed possible by my participation at 2023 ECE congress

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P52

Characteristics of hypoparathyroidism in a tertiary referral hospital

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Introduction
Hypoparathyroidism (HypoPT) is a rare endocrine disease characterized by abnormally low concentrations of PTH resulting in hypocalcemia. Etiologies are various and are dominated by postoperative HypoPT. HypoPT needs a lifelong treatment and follow-up in order to maintain appropriate calcium levels and prevent chronic complications.
Patients and Methods
A retrospective descriptive study was conducted at the endocrinology department in Fattouma Bourguiba University hospital.
Results
Twenty patients were included. The sex ratio was 1:3 with a mean age of 42.7 ± 17.9 years. The age at diagnosis was between 3 and 66 years. The main found etiologies were postsurgical hypoparathyroidism in 57.9% of patients, auto-immune in 26.3% and isolated genetic hypoparathyroidism in 15.7 %. Thyroid surgery was indicated for thyroid carcinoma (36.4%), multinodular goiter (34.6%) and Grave disease (27.2%). Auto-immune HypoPT was associated to Type 1 diabetes (60%), auto-immune thyroiditis (20%), Biermer's disease (20%) and coeliac disease (20%). The average calcium and PTH levels at diagnosis were respectively 2.07 ± 0.19mmol/l and 8.75 ± 6.43pg/l. All patients were treated by calcium carbonate with a mean daily dose of 3400 mg [1000-8000] along with active vitamin D analogs (alfacalcidol) with a mean daily dose of 1µg [0.25-2]. Twenty five percent of patients needed oral magnesium supplements.
Conclusion
To achieve treatment targets, the majority of patients with HypoPT, as shown in our study, require high doses of calcium and vitamin D supplements leading to multiple daily intake of medications that impair their quality of life.

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P297

Chronic hypoparathyroidism is associated with skeletal muscle dysfunction and restrictive lung disease

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Introduction
Whether patients with non-surgical hypoparathyroidism have skeletal muscle dysfunction is not studied. It is also not known if skeletal muscle dysfunction involves respiratory muscles and results in a restrictive lung disease (RLD).
Aim
To assess skeletal muscle and pulmonary function in patients with non-surgical hypoparathyroidism, who were asymptomatic for overt muscle and lung diseases.
Methods
Thirty patients with non-surgical hypoparathyroidism (mean age 37.7 years, 60% males) and forty healthy-controls were assessed for skeletal muscle function by hand-grip strength, short physical performance battery (SPPB) test, dual-energy x-ray absorptiometry, and electromyography. Pulmonary function was assessed in all by spirometry and diaphragmatic ultrasound. Those with a restrictive pattern on spirometry further underwent body plethysmography and diffusion lung capacity for carbon monoxide to confirm presence of RLD.
Results
Patients with hypoparathyroidism had lower levels of serum calcium (2.25 ± 0.15 vs 2.4 ± 0.12 mmol/l, $P < 0.001$), magnesium [median (interquartile-range) 0.74 (0.69-0.82) vs 0.78 (0.69-0.90) mmol/l, $P = 0.04$], hand-grip strength (18.08 ± 8.36 vs 22.90 ± 7.77 kg, $P = 0.01$) and SPPB score (9.5 [7-10] vs 12 [12-12], $P < 0.001$) compared to healthy-controls. Electromyographic evidence of myopathy was seen in 23% (5 of 22) patients with hypoparathyroidism, but none of the controls ($P = 0.08$). The proportion of patients with a RLD was higher in the group with hypoparathyroidism compared with controls (21% vs 0%, $P = 0.01$). Diaphragmatic excursion (4.22 ± 1.38 vs 5.18 ± 1.53 cm, $P = 0.01$) and thickness (3.79 ± 1.18 vs 4.28 ± 0.94 mm, $P = 0.05$) on deep inspiration were reduced in patients with hypoparathyroidism. Lean body mass was comparable in both the groups. In the multivariable analysis, the average of measurements of serum calcium in the previous year predicted hand-grip strength and SPPB score in patients with hypoparathyroidism.
Conclusion
Detailed testing of patients with hypoparathyroidism who were asymptomatic for overt muscle and lung diseases revealed significant impairment in parameters of skeletal muscle function. A substantial proportion of patients with hypoparathyroidism had electromyographic evidence of myopathy and RLD.

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P298

Localization studies in 443 patients with primary hyperparathyroidism by using a stepwise approach

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Objective
Primary hyperparathyroidism (PHP) is a common endocrine disorder diagnosed biochemically, common use of autoanalyzers increased the incidence of PHP throughout last decades. Minimally invasive parathyroidectomy has been preferred to the explorative surgical approach due to shorter operating time, lower complication rate, and smaller incision size. Thus localization studies have become very important. We aimed to investigate clinical and laboratory characteristics of patients, causes and success of localization studies in a large cohort of PHP in a retrospective manner.
Methods
Study included 443 patients with PHP diagnosed between January 2010 and January 2021. Clinic characterisrics, biochemical parameters, findings of imaging studies for localization and postoperative histopathological results were examined. Ultrasonography (US), US-guided PTH-washout analysis; ^{99m}Technetium -Sestamibi/^{123}Iodine Scintigraphy(MIBI -SPECT/CT) were used as initial localization techniques. Four Dimensional Computed Tomography(4D-CT), 18F-Fluorocholine Positron Emision Tomography (18F-FCH PET/CT) were used as advanced imaging methods for patients whose parathyroid lesions could not be localized with initial methods.
Results
79%($n = 350$) of patients were female, the mean age was 59.9 ± 13. Mean ± SD serum Calcium(Ca), Phosphate(PO_4) and Parathormone(PTH) levels were 10.9 ± 0.8 mg/dl, 2.7 ± 0.5 mg/dl and 192.7 ± 82.3 pg/ml, respectively. 12.9% of the patients had normocalcemic hyperparathyroidism. The incidence of osteoporosis was 42.6%($n = 150$). PTH levels were significantly higher in the patient group with osteoporosis($P = 0.017$). The most common surgical method was minimally invasive surgery at 81.2%. Histopathological evaluation resulted in single adenoma in 98.1% of patients and hyperplasia in 1.5%, cancer in %0.4. A significant positive correlation was found between adenoma volume with serum Ca and PTH levels ($P < 0.001$). The most common location of parathyroid lesions was right lower pole of thyroid gland with 49.6%. 4D-CT and 18F-FCH PET/CT were used in 60 and 43 patients, respectively. Positive predictive values(PPV) of imaging modalities: US, US-guided PTH-washout analysis, MIBI-SPECT/CT, 4D-CT and 18F-FCH PET/CT were 83.6%, 91.8%, 81.2%, 88.9% and 97.7%, respectively.
Conclusion
Calcium and PTH levels could give an idea for the size of the adenoma. Using initial localization studies (i.e US combined with PTH washout, MIBI-SPECT/CT) most of the adenomas could be localized. For those patients who required advanced imaging modalities, 4D-CT is highly effective, but 18-FCH PET/CT has the highest PPV for parathyroid adenoma localization.

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P299

Parathyroid hormone levels following denosumab therapy vs. zoledronic acid therapy for osteoporosis

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Background
Denosumab (DMAb) and zoledronic acid (ZA) are potent, anti-resorptive agents used to treat patients with osteoporosis. It has been suggested that they increase parathyroid hormone (PTH) levels in response to their antiresorptive effect, and that PTH elevation might be responsible for DMAb modeling actions on bone. The timeline and magnitude of PTH elevation post-DMAb and ZA has not been characterized in a large patient population.
Objective
To characterize PTH levels post-DMAb injection vs. baseline and vs. ZA injection.
Material and Methods
Female osteoporotic patients, $\geq$50 years, treated with DMAb or ZA, 2008–2020 were included if PTH was $<$1.5ULN before injection and if they had at least one PTH measurement 6 months after DMAb or 12 months after ZA injection. Exclusion criteria were creatinine $>$2mg/dl or diagnosis of hyperparathyroidism. Post-injection PTH levels were linked time-wise to previous injections.
Results
A total of 35,375 women, $\geq$50 years received DMAb or ZA for the first time in 2008–2020; 26,341 met the exclusion criteria. Of the remaining women, 5,640 received a first DMAb injection and 3,394 ZA. The DMAb group was older (73.2 vs. 69.8 years), was treated more frequently with osteoporosis medications before the injection (56.5% vs. 50.3%) and more had sustained a fracture (15.8% vs. 13.9%) compared to the ZA group. Vitamin D level was 80.9$\pm$21.9 nmol/l. Repeat PTH was available for 2,206 DMAb patients and 1,444 ZA. Among 772 PTH measurements in the first month post-DMAb, it was $>$1.5ULN in 156 (20.1%) and $>$2.5ULN in 74 (5.1%), whereas among 807 PTH measurements 5-months post-injection, it was $>$1.5ULN in 112 (13.9%) and $>$2.5ULN in 9 (1.1%). One-month post-ZA, PTH was $>$1.5ULN in 35/169 (20.7%) and $>$2.5ULN in 11 (6.5%), and decreased to $>$1.5ULN in 23/213 (10.7%) and to $>$2.5ULN in 2/213 (0.9%), 5 months after injection.
Discussion
This is the first study to examine PTH levels in a large population receiving DMAb or ZA injections, with precisely-timed PTH measurements post-injection. PTH levels increased by $>$1.5ULN in 20% of osteoporotic patients who received DMAb or ZA, while it increased to $>$2.5ULN in ~5% post-injection. PTH levels $>$2.5ULN declined gradually after treatment in both groups. It seems that PTH elevation is related to the antiresorptive effects of the drugs and is not a disease phenomenon. It is suggested to avoid checking PTH in the first few months post-DMAb and ZA therapy.

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P300

Bioluminescence and autofluorescence of parathyroid glands to identify an intra-thyroidal parathyroid tumour

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Bioluminescence is bringing new and exciting possibilities to the field of endocrine surgery, because we are able to better harness the property of autofluorescence of the parathyroid glands. Parathyroid glands have an inherent ability to produce infra-red autofluorescence at the wavelength of 820 nm to 830 nm, if the gland absorbs light at the wavelength of 750 nm. With highly sensitive technology and the ability to filter out other reflected light and noise, it is now possible to identify the infra-red light emitted by parathyroid glands and cells. We would like to share a case of primary hyperparathyroidism that could not be identified and localised pre-operatively, but a right thyroid nodule was identified. Intra-operatively, a neck exploration was strongly suggestive of an intrathyroidal parathyroid lesion in the known right thyroid nodule. With the aid of a specialised near infra-red (NIR) camera, autofluorescence was detected from the thyroid nodule, helping to confirm our preliminary diagnosis, and proceeded with a right hemithyroidectomy. Intra-operative measurement of the parathyroid hormone confirmed an adequate drop in the parathyroid hormone levels after the excision of the right hemithyroid. Post-operative pathological assessment also confirmed the presence of parathyroid tissue in the thyroid tumour. The accuracy of parathyroid gland detection can be greatly enhanced with the employment of highly sensitive NIR technology, and help shape the development better strategies to approach parathyroid surgery. Other applications of this technology in the setting of neck surgery will be discussed.

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P301

Healthcare resource utilization associated with post-surgical and non-surgical chronic hypoparathyroidism in England: A linked Clinical Practice Research Datalink, Hospital Episode Statistics, and Office for National Statistics retrospective analysis

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Background
Hypoparathyroidism, a rare endocrine disorder characterised by low serum calcium due to low or insufficient parathyroid hormone levels, most commonly occurs post-surgery although can also occur due to predisposing genetic conditions or idiopathically. Hypoparathyroidism requires long-term medical management to minimise complications and detrimental impacts on health-related quality of life. Few real-world studies, particularly in the UK, have quantified healthcare resource use (HCRU) associated with chronic hypoparathyroidism.
Aims
To describe demographic characteristics and HCRU associated with post-surgical and non-surgical chronic hypoparathyroidism, compared with matched controls without hypoparathyroidism, using a Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics (HES), and Office of National Statistics deaths registrations linked dataset.
Methods
Primary care data from CPRD linked to HES and death registrations in England, were used to retrospectively identify two adult hypoparathyroidism cohorts. The first, incident chronic hypoparathyroidism induced by surgery or radiotherapy between 01/04/2008–22/03/2019, with a look-back to 01/04/2007 to identify prior surgery or radiotherapy. The second, prevalent chronic hypoparathyroidism that was not surgically induced between 01/04/2008–22/03/2020. Both cohorts were indexed upon diagnosis of chronic hypoparathyroidism, defined as having two diagnosis codes 6-36 months apart or ongoing calcium or vitamin D analogue prescription in lieu of a second diagnosis code. Both hypoparathyroidism cohorts were matched with controls on age and gender. We estimated all-cause inpatient admissions and bed days per person per year (PPPY) for individuals with chronic hypoparathyroidism and those without.
Results
183 individuals with surgical and 447 with non-surgical chronic hypoparathyroidism were identified. Individuals in the post-surgical cohort were younger than those in the non-surgical (mean age: 53.3 vs 57.1 years) and a higher proportion were female (73.8% vs 62.7%). Over a median follow-up time of 56.5 months, individuals with post-surgical chronic hypoparathyroidism incurred more admissions (mean 14.1 PPPY vs 0.4 PPPY, mean difference 13.7, [11.9–15.5], $P<0.001$) and annual bed days (mean 7.9 PPPY vs 0.9 PPPY, mean difference 7, [5.4–8.8], $P<0.001$) compared to controls. The same trend was observed amongst individuals with chronic non-surgical hypoparathyroidism, who, over a median follow-up time of 44.9 months, had more admissions (4.5 PPPY vs 0.4 PPPY, mean difference 4.0, [2.9–5.6], $P<0.001$) and bed days (14.9 days PPPY vs 1.7 days PPPY, mean difference 13.2, [11.8-14.6], $P<0.001$) than controls.
Conclusion
Our results suggest that HCRU is significantly greater for individuals with chronic hypoparathyroidism compared to non-hypoparathyroidism controls, highlighting the need for effective treatment options in patients with chronic hypoparathyroidism.

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P302

Evaluation of Breast Calcification, Calcification Characteristics and BI-RADS (Breast Imaging-Reporting and Data System) Categories in Patients with Primary Hyperparathyroidism

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Aim
It is hypotethically thought that increased frequency of breast cancer in patients with primary hyperparathyroidism(PHPT)may be due to the fact that calcium accumulation in the breast may be higher in patients with PHPT giving rise to more breast-related examinations. Although there are many studies or case reports showing calcification in many organs and tissues, in PHPT, there is not any study investigating breast calcification in these patients in the literature. We aimed to determine the frequency and features of breast calcification and distribution of BI-RADS scores in patients with PHPT.
Method
Female patients $\geq$40 years old with PHPT and and age-matched healthy women were included. Demographical, antropometric and laboratory findings were noted. Mammography was performed in all patients and controls. Calcification types and BIRADS scores were recorded. Clustered microcalcification, ductal calcification, linear thin or segmental calcification were considered suspicious calcification. Skin calcification, scattered, punctate, vascular calcification and macrocalcification were termed as benign calcification. Two groups were compared in terms of demographical, laboratory findings, presence of calcification, calcification types and BI-RADS in mammography. Patients were divided in two groups according to the duration of PHPT as less or more than 48 months.
Results
Sixty-one patients and 75 control were enrolled. While age distribution was similar(57.0$\pm$7.9 vs 55$\pm$7.5, $P=0.153$), body mass index was higher in patient group(32.4$\pm$6.7 vs 29.2$\pm$6.2 kg/m^2, $P=0.005$). Median duration of PHPT was 46(1-85) months. BI-RADS score was comparable and the most frequent score was BIRADS-0. Presence of breast calcification and calcification types were not different in two groups. Demographical, laboratory and mammographic findings are summarized in table. Presence of calcification was similar in PHPT patients with disease duration of less and more than 48 months. There was not any cut-off for disease duration that can predict presence of calcification. Of the 3 patients(all was with PHPT)who underwent excisional breast biopsy, one resulted in invasive breast ca, one as atypical ductal hyperplasia, and the other as benign.
Conclusion
Female patients with PHPT did not have an increased incidence of breast calcification compared to healthy women, suggesting that calcification is not responsible for the increased incidence of breast cancer in these patients. Distribution of BI-RADS scores was also not affected by the presence of PHPT.

	PHPT ($n=61$, 44.9%)	Control ($n=75$, 55.1%)	p
Age	57.0$\pm$7.9	55$\pm$7.5	0.153
BI-RADS			
0	48 (77.7%)	58 (77.3%)	0.603
1	2 (3.3%)	4 (5.3%)	
2	9 (14.8%)	12 (16.0%)	
3	1 (1.6%)	0 (0.0%)	
4A	1 (1.6%)	0 (0.0%)	
4B	0 (0.0%)	0 (0.0%)	
4C	0 (0.0%)	1 (1.3%)	
Breast calcification	33 (54.1%)	42 (56.0%)	0.739
Benign calcification	30 (49.2%)	40 (53.3%)	
Suspicious calcification	3 (4.9%)	2 (2.7%)	
No calcification	28 (45.9%)	33 (44.0%)	

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P303

SPECT/CT parathyroid scintigraphy in primary hyperparathyroidism: minimizing the risk of negative results by biochemical parameters assessment

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Primary hyperparathyroidism (PHP) diagnosis in clinical practice is based on biochemical blood tests. Since a single parathyroid adenoma causes about 85% of cases, the treatment of choice is parathyroidectomy, preceded by imaging studies. Ultrasound and [^{99m}Tc]sestamibi scanning can enable adenoma localization. However, the latter method is of higher sensitivity, especially if combined with anatomical imaging. In some cases, the radiotracer uptake in adenoma tissue is insufficient, leading to negative imaging results. This study aimed to compare parathormone (PTH), calcium, and serum phosphate levels among patients diagnosed with PHP with positive and negative parathyroid nuclear hybrid imaging (SPECT/CT) and to evaluate biochemical parameters' ability to predict imaging results.
Results
563 patients with suspected primary hyperthyroidism (84% females, median age 62 years, IQR 19 years; 16% males, median age 59 years, IQR 25 years) who underwent [^{99m}Tc]sestamibi SPECT/CT imaging between 2010 and 2022, were included in this study. The imaging result was positive in 257 cases (46%). Patients with positive imaging were characterized by higher PTH (median 124.5 pg/ml vs 96.6 pg/ml; $P<0.05$), higher calcium (median 2.76 mmol/l vs 2.67 mmol/l; $P<0.05$), and lower serum phosphate concentrations (median 0.82 mmol/l vs 0.89 mmol/l; $P<0.05$). Based on ROC analysis, the following threshold values for nuclear imaging were proposed for calcium, PTH, and serum phosphate concentrations, respectively: calcium $\geq$3.11 mmol/l (AUC 0.73; PPV 72%; sensitivity = 37%; specificity = 88%); phosphate $\leq$ 0.45 mmol/l (AUC 0.65; PPV 55%; sensitivity = 36%; specificity = 79%); PTH $\geq$ 260 pg/ml (AUC 0,70; PPV 78%; SENS = 33%; SPEC = 92%).
Conclusions
Before offering preoperative hybrid nuclear imaging to a patient with PAH, attention should be paid to the results of biochemical tests to limit unnecessary radiation exposure. Indeed, if calcium and parathormone concentrations are slightly above the upper reference values, the probability of a negative imaging result seems to be high.

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P304

Evaluation of Laboratory Findings of Primary Hyperparathyroidism in Geriatric Patients

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Evaluation of Laboratory Findings of Primary Hyperparathyroidism in Geriatric Patients
Background
Primary hyperparathyroidism (PHPT) is an endocrine disease characterized by excessive secretion of parathormone (PTH) from one or more parathyroid glands. In recent studies, it has been reported that the PHPT clinic has turned into a largely asymptomatic disease in recent years. There are few studies on the effect of aging on laboratory findings of PHPT. We aimed to evaluate the laboratory findings of PHPT in the geriatric patient population and to determine the differences by comparing them with general PHPT patients in the current study.
Methods
A total of 182 patients operated on with the diagnosis of PHPT in our center between 2017-2019 were included in the current study. The patients' demographic, laboratory, and pathological data were recorded by scanning the files. Patients were divided into two groups as $<$65 years old and $\geq$65 years old.
Results
The patients comprised 149 females and 33 males with a mean age of 55.1$\pm$12.3 years. The full demographic and clinical data of the PHPT patients are reported in Table 1. No differences were found in serum PTH, calcium, phosphorus, alkaline phosphatase, creatinine, or 25-OH-D levels between the two groups. Urinary calcium levels were found to be significantly lower in geriatric patients. There was a significant negative correlation between urinary calcium level and age. The frequency of kidney stones was found to be less frequent in the geriatric patient group (12.9%& 32.1%, p:0.01). When postoperative transient hypocalcemia was evaluated, no significant difference was found between the two groups.
Conclusion
Clinical and laboratory findings of PHPT are affected by aging. Recent studies have shown that the disease is more often asymptomatic in the geriatric population than in young people and is characterized by a predominance of bone

Table 1 Demographic and laboratory data of primary hyperparathyroidism patients

Parameter	≥65 years (n:46)	<65 years (n:136)	*P*-value
Age (years)	70.9±4.9	49.7±9.1	**<0.001**
Gender (F/M)	40/6	109/27	0.30
Serum parathormone (pg/ml)	134.1 (76-764)	136 (71-922)	0.89
Serum calcium (mg/dl)	11.2±0.9	11.2±0.8	0.87
Serum phosphorus (mg/dl)	2.6±0.6	2.7±0.5	0.18
Urine calcium excretion (mg/day)	262 (101-646)	350.5 (108-1033)	**0.002**
Serum ALP (U/l)	103 (47-260)	109.5 (53-773)	0.30
Serum creatinine (mg/dl)	0.83±0.19	0.83±0.2	0.99
25-OH-D (ng/ml)	20.5±11.1	17.3±10.5	0.08
Adenoma weight (gr)	0.7 (0.12-5)	0.91 (0.1-10)	0.26

involvement. Clinical and laboratory findings of PHPT in geriatric patients may be better elucidated in multicenter studies involving larger patient populations.

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P305

A Phase 1/2, Open-Label, Multiple Ascending Dose Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of INZ-701 in Adults with ENPP1 Deficiency

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Background
ENPP1 Deficiency is a rare disorder due to inactivating mutations in the *ENPP1* gene. It is characterized by low levels of inorganic pyrophosphate (PPi), a critical regulator of mineralization; subsequent pathologic soft tissue calcification results in ~50% infant mortality and life-long musculoskeletal and cardiovascular morbidities. No targeted therapy exists for this disease. INZ-701 is a recombinant ENPP1-Fc investigational product.
Purpose
To determine the safety, tolerability, immunogenicity, pharmacokinetics and pharmacodynamics of INZ-701 following subcutaneous administration in adults with ENPP1 Deficiency.
Methods
Phase 1/2, multicenter, open-label, multiple ascending dose study including three cohorts of three adults each, with genetic confirmation and PPi <1300 nM (NCT04686175). Following ethical committee approval, participants were dosed at Day 1, then twice weekly from Day 8 through Day 32.
Results
In the first patient cohort receiving 0.2 mg/kg INZ-701, INZ-701 was well-tolerated with no serious adverse events or injection site reactions. A rapid (≤ 6 hrs) ~4-fold increase in PPi was noted in all three participants. Mean PPi increased from 262 $\pm$ 114 nM (screening) to a mean sustained level through Day 32 of 1374 $\pm$ 457nM (in the normal range), representing a ~5-fold increase in PPi. Steady state was reached approximately by Day 29 with a ~4-fold accumulation from Day 1, based on $AUC_{0\text{-}72hrs}$ and showed good correlation with INZ-701 activity. The half-life of INZ-701 (~126 hrs) suggests the potential for once-weekly dosing. Participants from the first cohort have enrolled in an open label extension study.
Conclusions
At the lowest dose studied, INZ-701 demonstrated a rapid and sustained increase in PPi levels in all participants, was well tolerated, and exhibited a favorable safety profile with a potential for once weekly dosing. Results from cohorts two (0.6 mg/kg dose) and three (1.8 mg/kg dose) are anticipated in early 2023.

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P306

Surgical fixation of ankle fractures with bioresorbable magnesium implants: A first-in-human HR-pQCT assessment of the implantation site

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Background
Bioresorbable implants should provide stability for fracture healing and resorb thereafter to make implant removal obsolete. Here, we report follow-up data of 6 patients treated with bioresorbable magnesium screws following medial malleolus fractures.
Purpose
Assessment of the implantation site and implant resorption of 11 implants in 6 patients with HR-pQCT (high resolution peripheral quantitative computed tomography).
Methods
Isolated, bimalleolar or trimalleolar ankle fractures were surgically treated with bioresorbable screws (Magnesium 99.1%, Calcium 0.45%, Zinc 0.45%) in 20 patients. After at least 2.5 years patients were clinical assessed and HR-pQCT-scans were performed. Screw residuals were evaluated in a binary approach for every axial slice generated by the HR-pQCT (residual present vs. not present). Evaluations included total volume, bone volume, and volume of the trabeculae-free space.
Results
All patients showed clinical evidence of fracture healing without clinical complications twelve weeks after the surgery. With full weight bearing and absence of pain in the fractured ankle. After 2.5 years, all observed implants were resorbed for the most part. Of 11 implants, 3 were dissolved without visible residuals. Minor residuals were present in 10% of slices (0%-33%). However, in 2 female study participants >50 years secondary expansions of the drilling channel were observed, where trabeculae were absent. Screw volume before implantation was 243.3 mm^3, and the trabeculae-free cavities were 596.1 mm^3 in mean size (239,2–1109,1mm^3) with the largest cavities in the bone with the lowest bone volume per total volume (BV/TV).
Conclusion
Bioresorbable magnesium screws for fracture fixation are providing fracture healing and satisfactory clinical outcome after one year. Surgical removal is not necessary. Especially in patients with decreased bone mineral density the dynamic and impact of implant resorption needs to be studied further.
Key words
HRpQCT, bioresorbable implant, magnesium screw, ankle fracture

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P307

FGF-23 levels in patients with normocalcemic primary hyperparathyroidism

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Introduction
Normocalcemic primary hyperparathyroidism (NPHPT) is a variant of primary hyperparathyroidism with consistently normal albumin-adjusted or free-ionized calcium levels. It may be an early stage of classic primary hyperparathyroidism or could represent a primary renal or bone disorder or result from another pathophysiologic mechanism leading to invariably elevated PTH levels.
Aim of the study
The study aims to check and compare the FGF-23 levels in three groups of patients: patients with PHPT, patients with NPHPT, and patients with normal calcium and PTH levels.
Methods
Our study included patients who were referred to the endocrinology clinic with a presumptive diagnosis of primary hyperparathyroidism, an isolated increased level of PTH, or reduced bone densitometry. For each patient, we performed blood analysis of FGF-23, calcium, phosphate, vitamin D [25(OH)D3], estimated

glomerular filtration rate (eGFR), bone turnover markers, and urine analysis for calcium/creatinine ratio.
Results
Our study included 105 patients. Thirty patients with hypercalcemic PHPT (HPHPT group), thirty patients with elevated PTH and normal calcium levels (NPHPT group), and 45 patients with normal calcium and PTH levels in the control group. FGF 23 level was 59.5 ± 23 pg/ml in the NPHPT group, 77 ± 33 pg/ml in the HPHPT group, and 49.7 ± 21.7 pg/ml in the control group ($P = 0.012$). The phosphate level was lowest in the HPHPT group: 2.9 ± 0.6 vs 3.5 ± 0.44 in the NPHPT and 3.8 ± 0.5 in the control groups ($P = 0.001$). No differences were found in eGFR, 25(OH)D3, C-terminal telopeptide type I collagen (CTX) and procollagen type 1 N-terminal propeptide (P1NP) levels, and bone densitometry scores between the three study groups. There was a significant positive relationship between PTH and FGF23 levels in two out of three groups of patients (HPHPT and NPHPT groups) when all three groups of patients were analyzed together ($P = 0.000$). A significant negative correlation was found between the FGF-23 level and GFR in all three study groups ($P = 0.023$).
Conclusion
Our findings suggest that NPHPT is an early stage of PHPT. Further studies are needed to determine the role of FGF-23 and its usefulness in NPHPT.

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P308

Therapeutic Options for Inoperable Local Relapse of Parathyroid Carcinoma with Symptomatic Hypercalcemia: a Case Report

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Introduction
Parathyroid carcinoma (PC) is an extremely rare malignancy. A complete surgical excision is often difficult, and persistent/recurrent disease occurs in up to 65% of cases. Progression often leads to symptomatic hypercalcemia, the major contributor to poor quality of life and mortality. Treatment options beyond surgical resection are limited. Denosumab is an approved therapy for refractory hypercalcemia of malignancy, and its use in unresectable PC has been described, with favourable results. The use of radiotherapy (RT) in PC has few reported cases in the literature, but could also serve as a valid alternative for inoperable local relapse. We present a case in which both denosumab and RT were used as palliative treatment approaches.
Case description
A 72-year-old women with unresectable recurrence of PC was admitted with severe hypercalcemia (15.5mg/dl) and acute kidney injury. Additional investigation revealed PTH = 1951pg/dl (9-72), obstructive nephrolithiasis and cervical lymph node metastases. Two weeks later, she underwent urgent palliative surgery due to refractory hypercalcemia, with marked improvement (calcium = 10.8mg/dl, PTH = 480pg/dl). 5 months later, she presented with symptomatic hypercalcemia (13.8mg/dl), despite therapy with zoledronic acid 4mg/month and cinacalcet 150mg/day. Cervical ultrasound confirmed tumour recurrence. Intravenous saline and bisphosphonate were, again, ineffective, with calcium nadir on the second day (11.6mg/dl) and subsequent increase (12.5mg/dl). Then, denosumab was started and calcium levels reduced on the third day (11.5mg/dl), with nadir on the seventh (10.8mg/dl). She was discharged under cinacalcet 180mg/day and denosumab 60mg/month. In the following months there were stable calcium levels (10.0-11.3mg/dl), despite ascending PTH levels (11993pg/ml). 6 months later she presented again with symptomatic hypercalcemia (13.8mg/dl). The multidisciplinary tumor board decided to opt for RT. It was delivered a radiation dose of 30 Gy in 10 fractions of 3 Gy, using an arc technique with 6 MV photons, at the cervical lesions. She tolerated well RT, and only developed grade I dermatitis. 3 months after RT, there was a progressive decrease in PTH (6453pg/ml) and calcium levels (9.7mg/dl). Currently, at 9-month RT-follow-up, calcium levels are within range (8.8-9.2mg/dl), and PTH levels are stable (4149-4858pg/ml), without further hospitalizations.
Conclusion
The approach to a relapse of PC remains a challenge. In inoperable cases, with severe hypercalcemia refractory to calcimimetic agents and bisphosphonates, treatment with denosumab may result in rapid reduction of calcium levels. As highlighted by this case, RT has also a role as a palliative treatment, with achievement of metabolic and symptomatic control of the disease.

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P309

Hyperparathyroidism in pregnancy, should we favour surgical intervention?

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Primary hyperparathyroidism (PHPT) during pregnancy is an uncommon condition that may have consequences for either mother, offspring, or both. Treatment can be either surgical or conservative.
The study aims
To compare maternal and fetal adverse outcomes between surgically (operated group) vs conservatively (non-operated group) treated mothers with gestational PHPT and to investigate the correlation between serum calcium and PTH values with complication rates.
Methods
A systematic review of all cases of PHPT during pregnancy, published in peer-reviewed English literature on PubMed and ScienceDirect from 1990 to 2021, was conducted.
Results
98 manuscripts were included in the study describing 368 cases of gestational hyperparathyroidism. 134 (36.4%) underwent parathyroidectomy, and 234 (63.6%) were treated conservatively. The mean age was 30.8 ± 5.5 and 31.6 ± 5.7, respectively. Median calcium levels were higher in the operated group, 12.2 mg/dl Vs. non-operated group 11.1 mg/dl ($P < 0.001$). PTH values had a mean of 132.5 pg/ml and 122.7 pg/ml for the respective groups ($P = 0.126$). Maternal and fetal complications were reported in 28.5% and 31% of cases. The rate of mild and moderate maternal complications was significantly higher in the operated group, reaching 50 (37.3%) compared to 40 (17.1%) in the non-operated group, respectively ($P < 0.01$). Fetal complications were significantly lower in the operated group. With 8.2% vs.13.7% for mild, 4.5% vs. 9.4% for moderate, and 1.5 vs. 12.4% for severe complications, respectively ($P < 0.001$). Favorable outcomes were obtained when the surgery took place during the second trimester. We identified a positive correlation between adverse maternal outcomes, serum calcium, and serum PTH values.
Conclusions
Parathyroidectomy seems to be favorable over conservative management when postoperative maternal and fetal complications are considered.

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Table 1: (Abstract P309) Comparison of the outcomes between the operated and non-operated groups.

Maternal complications	None	Mild	Moderate	Severe	NR	*P*-value
Total study population ($n = 368$)	263 (71.5%)	62 (16.8%)	28 (7.6%)	4 (1.1%)	11	<0.001
Non-operated group ($n = 234$)	180 (76.9%)	25 (10.7%)	15 (6.4%)	4 (1.7%)	10	
Operated group ($n = 134$)	83 (61.9%)	37 (27.6%)	13 (9.7%)	0	1	
Preoperative complications		24 (17.9%)	6 (4.4%)	0		0.23
Postoperative complications		13 (9.7%)	7 (5.2%)	0		
Fetal complications						
Non-operated group ($n = 234$)	140 (59.8%)	32 (13.7%)	22 (9.4%)	29 (12.4%)	11	<0.001
Operated group ($n = 134$)	114 (85.1%)	11 (8.2%)	6 (4.5%)	2 (1.5%)	1	
Combined groups ($n = 368$)	254 (69%)	43 (11.7%)	28 (7.6%)	31 (8.4%)	12	

Abbreviations: NR = severity not reported.

P310

The impact of a post hip fracture FLS on mortality and recurrent fracture - a tertiary medical center retrospective study

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Background
Rates of osteoporosis treatment following hip fractures are low. Fracture liaison service (FLS) has been shown to increase medical treatment for osteoporosis and decrease mortality. The aim of our study was to assess the impact of in hospital FLS on mortality and second hip fracture.
Methods
This retrospective study included patients over 65 years of age, insured by "Clalit" health service who were admitted to Soroka University Medical Center (SUMC) for rehabilitation at the Geriatrics department following the surgical repair of hip fracture. We compared rates of the composite outcome of mortality and/or second hip fracture in two equal time periods: before and after the implementation of SUMC FLS. Data were captured from the electronic medical charts including mortality, demographics, medical history, drug purchase and lab before and after hip fracture.
Results
319 and 667 patients fulfilled study criteria in the pre and post FLS periods, respectively. Baseline characteristics of both cohorts were similar excluding eGFR that was lower and rates of PPI and steroid use that were higher in the FLS cohort. Rates of endocrine consultation (93.4% vs 3.4% $P<001$), performance of DXA-BMD scan (42.3% vs. 7.5% $P<0.001$), parenteral anti osteoporosis treatment (65.2% vs 3.1% $P<0.001$) were higher in the FLS cohort, while use of oral bisphosphonates was lower (26.1% vs 56/4% $P<0.001$). Multivariable cox regression adjusted for age, comorbidities (expressed as the Charlson comorbidity index) and FIM (functional independence measure) score, demonstrated that the implementation of the FLS decreased the composite outcome of recurrent hip fracture and mortality only in patients under age 80 OR 0.55 (95% CI 0.36-0.83; $P=0.004$).
Conclusions
Implementation of in hospital post hip fracture FLS increased rates of endocrine consultation, performance of DXA BMD and rates of parenteral treatment for osteoporosis. The FLS decreased the composite outcome of mortality and second fracture among patients under age 80.

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P311

Hypocalcemia and pulseless electric activity revealing chromosome 22q11.2 deletion syndrome in the midst of a conglomerate of potential etiologic factors

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Background
Chromosome 22q11.2 deletion syndrome has been reported in about 1 per 347 to 992 living births. Hypocalcemia occurs in up to 80.4% of cases.
Case description
A 28-year-old man, known with autism spectrum disorder (ASD), presented at the emergency department (ED) for limbs muscle cramps. Medical history included chronic myeloid leukemia treated with tyrosine kinase inhibitor (TKI) the last 10 years, gastric bypass and recurrent fractures due to osteoporosis managed by alendronate. The preceding four months, alendronate was switched to zoledronate because of digestive adverse effects. After administration of zoledronate, the patient experienced exacerbation of the muscle stiffness. At the ED, upper limbs spasms (Trousseau's sign) hindered blood pressure measurement. Shortly after arrival, the patient suddenly developed pulseless electric activity, requiring advanced cardiopulmonary resuscitation, endotracheal intubation and admission to the intensive care unit. Investigations revealed a long QTc at 513 msec, severe hypocalcemia (ionized Ca 0.66 mmol/l [range 1.17-1.33]), normal magnesium, hypophosphatemia (0.49 mmol/l [0.78-1.42]), normal vitamin D and inappropriately low parathyroid hormone (PTH) level (38 ng/l [range 7-70]). Low calcium level was recorded immediately after initiation of TKI ruling out gastric bypass and biphosphonate as primary etiologic factors. Genetic testing was requested based on inappropriately low PTH, asymmetric crying facies, mild epicanthal fold and malar flatness. Deletions of chromosome 22q11.2 spanning catechol-O-methyltransferase *(COMT)* and T-box transcription factor 1 *(TBX1)* genes locations were identified. Upon discharge, calcium level improved under oral calcium, magnesium and calcitriol. TKI and biphosphonate were interrupted.
Discussion
In our patient, identification of chromosome 22q11.2 deletion confirmed a constitutional defect in calcium metabolism, which might have been sequentially exacerbated by initiation of TKI, gastric bypass and biphosphonate. Hypocalcemia in DiGeorge syndrome results from hypoparathyroidism and could occurs not only in the neonatal period, but also in adulthood. Other clinical characteristics of the disease encompass cardiac defects, abnormal facies, thymic hypoplasia, cleft palate (CATCH-22). While ascertainment of *TBX1* deletion relates to hypoparathyroidism that of *COMT* gene could be associated to psychiatric defects including ASD and psychosis.
Conclusion
This case highlights the diagnostic complexity of hypocalcemia in a setting of multiple potential etiologic factors. It raises the call to keep in mind that chromosome 22q11.2 deletion syndrome is not that uncommon and can be revealed in adulthood. Specific phenotype, specifically in the setting of hypocalcemia in a patient with inappropriately low PTH, should prompt clinicians to order genetic testing independently of the patient's age.

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P312

Teriparatide in the challenging management of hypoparathyroidism, our experience in one medical center in Argentina

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Hypoparathyroidism is an endocrine deficiency whose substitution treatment with PTH 1-84 is only available in compassionate use in Argentina. There is a subgroup of patients in which the conventional therapy with calcium, calcitriol, phosphorous chelators, magnesium and diuretics does not reach an adequate clinical and/or biochemical compensation. Although teriparatide (PTH 1-34) is not approved for patients with hypoparathyroidism, it is a plausible therapeutic resource.
Objective
To show our experience in the use of teriparatide in patients with primary and secondary hypoparathyroidism.
Material and Methods
Retrospective study, we assessed the medical records of 8 patients with hypoparathyroidism who were treated with teriparatide, 2 with primary-idiopathic

Lab tests	Pre-Teriparatide (mean)	Post-Teriparatide (mean)	p
Calcemia (mg/dl)	6.9	8.17	**0.023**
Phospathemia (mg/dl)	5	4	**0.009**
Calciuria (mg/24 hs)	141	313	0.131

Table 1 (Abstract P312)

TREATMENT	Daily doses (mean)		Quantity of pills (mean)		% of decrease
	Pre-Teriparatide	Post-Teriparatide	Pre-Teriparatide	Post-Teriparatide	
Calcium carbonate g/d	2.5	0.8	5.1 (4-12)	1.7 (1-5)	67%
Calcium citrate g/d	1.9	0.9	6.2 (2-10)	2.8 (1-6)	55%
Calcitriol ug/d	0.5	0.25	2 (1-3)	1 (1-3)	50%
Total *			15 (9-28)	7 (1-14)	53%

*Diuretics, magnesium and Vitamin D were included

and 6 post-thyroidectomy. Six women, mean age: 41.8 years (34-56), time of diagnosis: 10.9 years (2-40). The main cause to prescribe teriparatide was symptomatic hypocalcemia in 4 patients and hypocalcemia in their lab tests in the other 4; all of them with high doses of medication, negative impact in their quality of life and some needed multiple hospitalizations because of hypocalcemia. We assessed the doses of carbonate and citrate of calcium, calcitriol and diuretics before and after 6 months of teriparatide, clinical response, lab tests outcomes and follow-up.
Results
Of the six patients with post-surgical hypoparathyroidism, 4 had papillary thyroid carcinoma, 1 multinodular goiter and 1 Grave's disease. The dose of teriparatide was 20 mg in 7 and 40 mg in 1, mean time of treatment: 3.45 years (0.8-7). The decrease in medication could not be assessed in one patient because it was necessary to start the treatment with teriparatide immediately after thyroid surgery. Conclusions: The treatment with teriparatide achieved significant and steady improvement in the values of calcium and phosphorus in most patients. The daily intake of carbonate and citrate of calcium, and of calcitriol decreased about 50%. Teriparatide treatment avoided frequent hypocalcemia-related hospitalizations. Long-term safety studies are necessary when teriparatide is used as an alternative to PTH 1-84.

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P313

Permanent Hypoparathyroidism Consecutive to Thyroidectomy: Clinical Characterization in a Tertiary Center in Quito-Ecuador

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Background
Acquired hypoparathyroidism due to thyroid surgery for thyroid cancer is the most common postsurgical etiology in a tertiary health center in Ecuador. Therefore, the data published from our country is limited. An observational cross-sectional study was carried out to determine the clinical, biochemical and therapeutic characteristics of patients with permanent hypoparathyroidism in the endocrinology department.
Results
102 patients were included in this trial, 96.1% were women. In the patients with suspected thyroid cancer (75.49%), the detection of nodules was incidental in a 13.73%. Total thyroidectomy without lymph node dissection was performed in 54.9%, thyroidectomy plus central dissection in 41.18%, and total thyroidectomy with right or left lateral dissection in 3.92%. The most prevalent definitive diagnosis was the one associated with malignancy in 61 patients (59.80%), and 98.3% of those due to papillary carcinoma. Tumor size in 57.38% was greater than 2 cm. Lymph node metastases occurred in 49.18%, with more than 5 nodes in 33.33%. According to the operating protocol, parathyroid resection was reported in only one patient (1.64%), however, in 19 (31.15%) there was no description of this data. During follow-up the clinical characteristics were variable. 21.57% were asymptomatic and 78.43% presented one or more of the following symptoms or signs: limb paraesthesias (44.36%), Chvostek's sign (25.56%), Trousseau's sign (11.28%), facial paresthesias (7.53%), spontaneous tetany (4.5%), arrhythmias (1.5%), fatigue (1.5%), laryngospasm (0.75%). Calcium carbonate supplementation in 67.4% of the patients was maintained at a dose between 1500 and 3000 mg/day, in 31.37% lower doses between 500 and 1000 mg/day were needed, only in 3.92% higher doses were necessary, equal or greater at 4000 mg/day. Regarding calcitriol, 33.33% were not supplemented with this drug, in the rest of the patients the most common dose was 0.5 to 1 mg/day. An association was found between suboptimal clinical control of hypoparathyroidism and patients who had more than 1 surgery ($P=0.046$). There was also an association between a tumor size greater than 2 cm and the requirement of calcium doses greater than 1500 mg/day ($P=0.001$).
Conclusion
The characterization in our study showed several similarities with those reported in the literature. Future research is needed to determine the impact of the disease on the quality of life of the people affected, establish costs and improve the use of resources and optimize interventions in our patients.
Key words
Hypoparathyroidism, postoperative, thyroidectomy, calcium, calcitriol.

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P314

PTH increasing with BMI associated with cortical bone density

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Objective
The goal in this study was to evaluate serum parathormone (PTH) and 25-hydroxy-vitamin D (25OHD), calcium levels and bone mineral density (BMD) in patients with obesity and determine the relationship between biochemical bone parameters, body mass index (BMI) and trabecular/cortical BMD over a wide range of body weights.
Methods
We examined 337 women (mean age 41.35 years old; BMI 45.47 kg/m^2) who were classified into three categories of BMI 30-40, 40-50, 50-60 including obese-class I-II (BMI 30-34.9 and BMI 35-39.9) and obese-class III (BMI>40). Bone mineral density (g/cm^2), trabecular, and cortical bone components were measured by dual energy *X*-Ray absorptiometry; and calcium, PTH, and 25OHD were analyzed.
Results
Mean age was similar among the BMI groups. PTH levels were significantly higher in BMI group 2 and 3 than group 1 ($P=0.003$), though 25OHD and calcium levels were not significantly different among the groups ($P=0.82$,0.052; respectively). Postmenopausal women with obesity had lower cortical BMD than premenopausal women ($P<0.001$). There was a negative correlation between PTH levels and cortical BMD ($P=0.001$). Menopause status, BMI and PTH but not age were the predictors for cortical BMD (R2= 0.346, $P<0.001$) (Table-1).
Conclusion
Increased PTH levels were seen in patients with higher BMI without a significant difference in calcium and 25OHD levels. PTH was negatively associated with cortical BMD. Whether or not PTH levels in obesity influences fracture risk needs to be further explored[1, 2].
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Table 1: Regression analysis prediction cortical bone mineral content in total cohort

	Beta coefficient (B.C.)	Sig.	95% confident interval for B.C.	
			Lower Bound	Upper Bound
Menopause Status	-0.264	<0.001	<0.104	-0.043
PTH	-0.264	<0.001	<0.104	-0.043
BMI	0.126	<0.027	<0.000	0.006

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P315

Study on prevalence of hypercalcemia due to chronic liver disease and correlation with its severity

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Introduction
Chronic liver disease (CLD) is usually not described as a common cause of hypercalcemia unless there is hepatoma. Of late, there are some reports suggesting CLD as a cause for hypercalcemia. The exact mechanism contributing to hypercalcemia in CLD is poorly understood. It usually correlates with the severity of disease.
Aim of the study
To assess the prevalence of hypercalcemia in patients with chronic liver disease
To study the relation of hypercalcemia to the severity and duration of chronic liver disease.
Materials and Methods
Patients getting hospitalised with chronic liver disease in a tertiary referral centre between 2016 and 2018 were included in the study. Patients with known hypercalcemic disorders, malignancies and those on active Vitamin D supplements were excluded. Besides Liver function tests, Prothrombin time and AFP, Corrected Calcium estimation was done in all patients. In patients who had corrected Calcium>10.5 mg/dl, Parathyroid hormone and Vitamin D assays were performed. Patients who were found to have hypercalcemia were followed up for next 1 year.

Results
251 patients participated in the study. 24 patients (9.6%) was found to have hypercalcemia. 3 /24 had hyperparathyroidism. In the rest, 21 patients, no definitive etiology was found. Hypercalcemia was attributed to chronic liver disease. Majority of the patients (76%) in the hypercalcemia group had Child C score, while only 25% in the non hypercalcemia group had Child C score. The mean bilirubin level was significantly high in hypercalcemic group when compared to non hypercalcemic group (6.67mg/dl vs 2.16 mg/dl). There was no significant renal dysfunction among patients with hypercalcemia compared to patients with normocalcemia.
Conclusion
Hypercalcemia is fairly common among patients with advanced CLD. It correlates well with the severity of liver disese and bilirubin levels.

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P316

Influence of musculoskeletal status on fracture risk in patients with adult hypophosphatasia

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Introduction
Hypophosphatasia (HPP) is an inherited disease, characterized by a non-tissue-specific alkaline phosphatase deficiency that leads to abnormal mineralization of bone tissue, which promotes fragility fractures. A defective muscle status could have important clinical repercussions on fracture risk. The aim of this work was to evaluate the relationship between bone and muscle compartment.
Material and Methods
Observational cross-sectional study in adults with PPH. Demographic (age, sex), analytical (alkaline phosphatase (ALP), normal range: 30-120 U/l), and clinical variables (fractures, kilograms (kg) of muscle strength with Jamar dynamometer -cut-off point: <p10 of Spanish population-, rectus femoris quadriceps muscle mass with ultrasound -Sonosite S-Nerve®- and bone mineral density with dual energy X-ray absorptiometry expressed according to T and Z-score. Statistical analysis was performed with IBM SPSS v.25.
Results
Twenty-one subjects were studied. 54% women, mean age: 49 ± 18 years. The mean FA was 28 ± 12U/l. 41% presented at least 1 bone fracture. Mean dynamometry was 28 ± 11kg, 100% with good muscle strength. In the nutritional morphological assessment, the mean Y-axis measurement was 1.5 ± 0.7 and muscle area, 4.8 ± 2.5. The mean T-score in lumbar spine (L1-L4) was -0.8 ± 1.5 and in femoral neck (FC) -1.3 ± 0.9. The mean Z-score in L1-L4 was 0.08 ± 1 and in CF 0.06 ± 1.1. Muscle strength was positively correlated with Y-axis ($r=0.52$, $P=0.02$), with muscle area ($r=0.51$, $P=0.02$), with T and Z-score in CF ($r=0.64$, $P=0.002$) and with T and Z-score in L1-L4 ($r=0.51$, $P=0.02$).
Conclusions
There is a high prevalence of fractures in patients with PPH. A positive correlation was observed between the muscle and bone compartments. Therefore, enhancing the muscle compartment in PPH patients could reduce the risk of fracture in these patients.

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P317

Calcinosis cutis as a rare manifestation of primary hyperparathyroidism: a case report

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Background
Calcinosis cutis is a rare manifestation characterized by calcium deposits in the skin and subcutaneous tissues, mostly found in auto-immune diseases. A case of calcinosis cutis (on the vertex and the face) associated to hyperparathyroidism is presented. We discuss the etiology, diagnosis and management of this rare condition, along with a short review of the literature
Case presentation
We report a case of calcinosis cutis with primary hyperparathyroidism. A 77 year-old woman initially presented a rash associated with a severe pruritus responsible for significant impact on quality of life. The rash was only located on the vertex, the face and the ears and associated to externalization of small grains and filaments. She also presented a hypercalcemia due to primary hyperparathyroidism. It was a moderate hypercalcemia (average 2.85 mmol/l) with PTH 100 ng/l (N 15-65). The renal assessment was normal and the bone mineral density (BMD) was subnormal (femoral neck Tscore -1.7 and lumbar Tscore -2.1). The morphological assessment found an ectopic parathyroid adenoma of 15 mm near the thyroid cartilage. The patient had a cutaneaous biopsy of the calcinosis and the anatomopathological analysis did not found any specific element of calcinosis. The analysis of the small grains stated they were calcium grains.. No auto-immune or infectious cause was found (ANCA, ANA, anti Sm, anti-RNP, anti SSA SSB, HIV, HBV and HCV serologies, and parasitological stool examination). We assumed that it was a cutaneous manifestation of the primary hyperparathyroidism; although it is extremely rare. We reported less than 5 cases in the literature and most of them had calcinosis cutis due to secondary hyperparathyroidism; only one case had primary hyperparathyrodism. By performing a neck surgery to remove the parathyroid adenoma, the calcemia normalized immediately while it took around 3 months to see a favorable evolution of the calcinosis.
Conclusion
Although, calcinosis cutis is rarely associated to primary hyperparathyroidism, it should be evoked in patients with a negative auto-immune or infectious assessment, with a hypercalcemia due to hyperparathyroidism and a rash. If the diagnosis of calcinosis cutis is confirmed in these patients, the surgery of the parathyroid adenoma enables a favorable, although slow, evolution.

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P318

Rare association of primary hyperparathyroidism with type 3 multiple autoimmune syndrome

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Introduction
Primary hyperparathyroidism (PHPT) is most commonly sporadic and in rare circumstances, it can develop as part of multiple endocrine neoplasia (MEN). There are few cases described in the literature reporting an association of PHPT with myasthenia gravis and multiple autoimmune syndrome (MAS). These patients may present only with clinical signs of PHPT making it difficult to suspect the coexistence of MAS. Here, we report the case of type 3 MAS in a woman with PHPT due to a parathyroid adenoma.
Observation
A 53-year-old female patient consulted our department for asthenia. She had hypothyroidism due to Hashimoto's thyroiditis, treated with levothyroxine. She had also pernicious anemia treated with vitamin B12 replacement. Her TSH and hemoglobin levels were within the normal reference range. The diagnosis of PHPT was made after a phosphocalcic assessment showing the association of hypercalcemia at 2.89 mmol/l (2,25-2,65 mmol/l) with hypophosphatemia at 0.77 mmol/l (0,8-1,2 mmol/l) and elevated PTH level at 95 pg/ml (10-65 pg/ml). Morphological and functional exams confirmed a right inferior parathyroid adenoma. screening for MEN was negative. She underwent parathyroidectomy and kept a normal serum calcium level (2.28 mmol/l) during the follow-up. The patient was still asthenic with onset of skeletal muscle weakness leading to the diagnosis of myasthenia gravis. Her acetylcholine receptor antibodies levels were positive (1.2 mmol/l; reference range: <0.5 nmol/l).
Discussion
The coexistence of myasthenia gravis with autoimmune thyroid disease and pernicious anemia is well-recognized as type 3 MAS. PHPT is known to be associated with MEN and only few cases reports mentioned its presence with myasthenia gravis and thymoma. Screening for thymoma is necessary since it is present in 15% of myasthenia gravis cases and since thymus and parathyroid glands have common embryologic origin.

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P319

Unexpected first finding in primary hyperparathyroidism; peripheral giant cell granuloma in the mandibula

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Aim and Introduction
Peripheral giant cell granulomas (PHDG) are uncommon exophytic lesions of the oral cavity that originate from the periosteum or periodontal membrane as a polypoid mass. Mandibular involvement is more common than maxillary involvement. Patients with primary hyperparathyroidism can infrequently exhibit PHDG in the early stages of the disease. We wanted to present our case who was examined for giant cell granuloma developing in the mandibula and was found to have parathyroid adenoma.
Case
A 47-year-old female patient with no known history of systemic disease applied to an external center due to swelling in the gingiva. The patient applied to us after a biopsy was taken due to a bone cyst detected at the level of the left second premolar tooth, and a giant cell granuloma that was detected. The patient's creatinin was 0.5 mg/dl (0.51-0.95), PTH level was 163.9 ng/l (12-88), calcium was 10.1 mg/dl (8.8-10.6), phosphorus was 2.8 mg/dl (2.5-4.5), vitamin D was 10 ug/l (30-100), Alcaline Phosphatase was 182 U/l (30-120) and albumin was 41 g/l (35-52). On the ultrasonography of the thyroid, a 3x4x7 mm hypoechoic nodular formation compatible with a parathyroid adenoma was observed in the inferior right thyroid lobe. SESTAMIBI parathyroid scintigraphy revealed a nodular lesion compatible with adenoma. Excision of a parathyroid adenoma was planned for the patient. In the inferior right lobe, a 1x0.5 cm mass consistent with an adenoma was removed. PTH decreased to 53 ng/l 15 minutes after specimen extraction in the patient whose pre-operative PTH was 161 ng/l. The macroscopic appearance of the specimen was reported as a 0.5 g weight, uniformly encapsulated yellow-brown nodular excision material. A peripheral giant cell granuloma developing in the jaw in a patient with normocalcemic primary hyperparathyroidism was evaluated as an early complication of the disease.
Conclusion
Giant cell granulomas that develop in peripheral bones such as the jaw may also occur in the early stages of the disease, and it should not be forgotten that they may be the first sign of the disease. Patients with giant cell granuloma in the oral cavity should be examined for hyperparathyroidism even if the calcium level is normal. Although there is no definitive treatment protocol, parathyroid adenoma excision can be performed.

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P320

Evaluation of bone impact in a population of patients with Cushing's disease

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Introduction
Osteoporosis is a well-recognized complication of Cushing's disease (CD). It results from a combination of systemic and local effects that glucocorticoids have on bone and mineral metabolism. The prevalence of osteoporosis due to excess endogenous cortisol has been reported at 50-59%, trabecular bone is more severely affected in CS than cortical bone.
Goal of the study:
To assess the prevalence of bone involvement in patients with Cushing's disease.
Patients and methods
This is a retrospective study of a sample of 69 patients with ACTH-dependent Cushing's disease, collected between (January 2000–December 2022), followed in the endocrinology department of Bologhine. We excluded patients with exogenous Cushing's syndrome and a history of metabolic bone disease and systemic disease such as rheumatoid arthritis, bronchial asthma, or a history of taking bone-affecting antiepileptic drugs. BMD was measured by dual-energy X-ray absorptiometry (DXA) at the level of the lumbar spine (L1–L4, AP) and femur, recorded in terms of absolute mineral content in g/cm ^{2} and Z -score, T-score at both sites.
Results
On a sample of 69 patients: The average age is 43 years, with a sex ratio of 4/1 (4 F, 1 M). Only 43 patients among them (69) benefited from a BMD. Osteoporosis is found in 48.8% of patients, osteopenia in 39.5% and only 11.6% of the cohort have normal BMD. Severe osteoporosis, ie osteoporosis associated with a bone fracture, was present in 3 cases with case of vertebral compression. The Z-score values were significantly lower at the vertebral level with an average of (-1.9) than at the femoral level with an average of (-1.1) ($P=$ 0.001). The difference in BMD was not significant between patients without cycle disorders and oligo-/amenorrhoeic patients with Cushing's disease. (P-value: 0.43) We found a negative correlation with morning plasma cortisol and BMD at the vertebral level ($r^2 = 0.22$, $P=$ 3.55X 10^{-15}) and at the hip ($r^2 = 0.13$, $P=$ 5.25X10^{-15}) although that is not statistically significant.
Conclusion
Our study clearly showed that vertebral BMD in patients with Cushing's disease is more affected than femoral BMD. Osteoporosis must therefore be systematically sought and treated in order to avoid these complications which can compromise the prognosis.

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P321

Severe persistent hypocalcemia and hungry bone syndrome after parathyroidectomy in a patient with giant parathyroid adenoma and concurrent osteoblastic bone metastasis from prostate cancer

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Introduction
Hungry bone syndrome (HBS) is a rare condition that can appear after surgery for hyperparathyroidism, characterized by hypocalcemia, hypophosphatemia, low calciuria, especially in patients with severe primary hyperparathyroidism, bone lesions and elevated alkaline phosphatase. We present a case of severe persistent hypocalcemia after resection of a giant parathyroid adenoma in a patient with concurrent osteoblastic bone metastasis from prostate cancer.
Case report
A 60 year-old man, who recently underwent surgery for prostate adenocarcinoma, was admitted with newly diagnosed parathyroid adenoma identified during his oncological follow-up. He described generalized weakness, intense back-pain and constipation. Personal history includes gastric resection with gastroenteroanastomosis. Blood tests showed hypercalcemia of 13.6 – 14 mg/dl, normophosphatemia 2.6mg/dl and high alkaline phosphatase of 555U/l, high parathyroid hormone (PTH) 605 pg/ml and bone turnover markers: C-telopeptide 3.32ng/ml, P1NP 1168 ng/ml, osteocalcin 304 ng/ml. Medical treatment with intravenous Zoledronic acid, rehydration, pain relievers was initiated. Full-body CT scan revealed a large right-inferior parathyroid adenoma and multiple osteosclerotic lesions. Parathyroidectomy was performed and histopathological examination confirmed an 9 g and 37/18/19mm parathyroid adenoma. The postoperative period was characterized by severe hypocalcemia (range between 6.6-8.24 mg/dl), hypophosphatemia (range between 1.9-2.6 mg/dl), normal PTH, and also an inflammatory syndrome with acute pain due to chondrocalcinosis crisis of 1st left metatarsophalangeal joint and left knee joint. The patient was discharged with improved clinical and biochemical features on high doses of citrate-calcium and calcitriol.
Conclusion
This case reflects the rare occurence of many mechanisms concurring to hypocalcemia: hungry bone syndrome, osteoblastic metastasis and gastric resection.

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P322

Clinical profile of primary hyperparathyroidism patients in a tertiary endocrine center in Kathmadu, Nepal

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There is limited data on primary hyperparathyroidism in Nepal. We did a retrospective study, where we analyzed data of sixteen patients who presented in our endocrine clinic from January 2016 to December 2022. Among them 10 patients (62.5%) were female and 6 (37.5%) were male. The mean age of the patients was 53.88 +/- 17.72 years ranging from 24 to 82 years. The mean BMI of the patients was 28.38 +/- 5.22 kg/m^2. The most common presenting features were bone and joint pain (38.89%) followed by fatigue and muscle weakness (33.33% each). Renal calculi were present in seven cases (38.89%). Two patients (12.5%) had acute pancreatitis. Hypertension was present in 50% of the cases and diabetes was present in 2 cases only (12.5%). DEXA san was done in 4 patients (25%); one

patient had osteoporosis and two had osteopenia. No patient had fragility fracture. Mean eGFR was 73 +/- 21.10 ml/min/1.73 m2. The mean corrected serum calcium concentration was 12.12 +/- 2.65 mg/dl. The mean serum 25(OH) Vitamin D concentration was 24.05 +/- 13.55 ng/ml. The mean parathyroid hormone was 342.56 +/- 231.35 pg/ml ranging from 81.80 pg/ml to 926.90 pg/ml. Serum phosphorus level was investigated in fourteen patients and the mean phosphorus level was 2.80 +/ 0.76 mg/dl. 24hr urinary calcium was evaluated among 10 patients and the mean was 295.07+/-133.67 mg. Ultrasonography of neck was done in thirteen patients; among them parathyroid adenoma was seen in 10 patients (76.92%). Sestamibi scan was done in all patients which showed parathyroid adenoma in thirteen patients (81.25%) and in three patients (18.75 %) there was no evidence of parathyroid adenoma. Seven of them (53.84%) had left inferior parathyroid adenoma whereas five (38.46%) had right inferior parathyroid adenoma and one (7.69%) patient had left superior parathyroid adenoma. Ten patients (62.5%) underwent surgery to remove parathyroid adenoma. Six patients (37.5%) refused surgery. Patients who refused surgery received Cinacalcet. Before surgery, two patients received IV Zolendronic acid. Postoperatively the mean PTH was 39.32 +/- 27.29 pg/ml ranging from 2 to 126 pg/ml. The mean corrected serum calcium was 9.13 +/- 0.82 mg/dl and the mean serum phosphorus of seven patients was 2.9 +/- 0.38 mg/dl.

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P323

Epidemiologic, clinical and biological aspects of primary hyperparathyroidism: About 107 cases

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Introduction
Primary hyperparathyroidism is one of the most common endocrinopathies with an estimated prevalence in the general population of 1 to 6/1000.
Objective
To describe the epidemiological, clinical and biological characteristics of patients with primary hyperparathyroidism.
Patients and methods
Retrospective descriptive study, including patients hospitalized in the Endocrinology Department of the Ibn Rochd University Hospital of Casablanca from January 1988 to December 2022. The data collection was carried out with the help of the patients' files, the data collected are the following: age, sex, pathological history, history of the disease, clinical examination, paraclinical examination, management, histological study of the operative part as well as the postoperative evolution. The analysis of the files was done with SPSS software.
Results
The mean age was 52.7 years (10-78), the sex ratio M/F was 0.16. Symptomatology was dominated by bone pain (63%), pathological fractures (42%) and digestive disorders. The mean blood calcium level was 126.19 mg/l. The 24-hour calciuria was elevated in 27 patients. The mean phosphorus level was 21.16 mg/l. Mean PTH was 993.11 pg/ml. The data from our study showed vitamin D deficiency in 83 with a mean Vit D level of 14.09 ng/dl. The average duration of symptoms was around 24 months. Pathological fracture was found in 46 patients, digestive disorder in 17 patients, renal lithiasis in 17 patients and vesicular lithiasis in 4 patients. 96 patients underwent cervical ultrasound, which revealed a parathyroid nodule in 78 cases. Scintigraphy was performed in 31 cases showing pathological fixation in 24 cases. CT scans were performed in 65 patients and revealed a parathyroid adenoma in 51 cases. 89 patients underwent surgery, with associated thyroid surgery in 49 patients. Pathological examination showed parathyroid adenoma in 76 cases, parathyroid hyperplasia in 10 cases and parathyroid carcinoma in 2 cases.
Conclusion
Primary hyperparathyroidism is a frequent endocrinopathy with clinical polymorphism, the main etiology being parathyroid adenoma. The main complications were pathological fractures and renal lithiasis.

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P324

Non-genetic, non-pharmacologic risk factors for osteoporosis: an umbrella review of observational studies

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Introduction
Osteoporosis is a prevalent skeletal disease associated with increased fracture risk, morbidity, and mortality. Several meta-analyses have investigated the association between non-genetic, non-pharmacologic factors and osteoporosis risk.
Purpose
We aimed to perform an umbrella review of the literature to systematically evaluate the available evidence.
Methods
Meta-analyses of observational studies evaluating the association between non-genetic, non-pharmacologic factors and osteoporosis risk in mainly adult populations were identified by searching MEDLINE (via PubMed), Scopus and CENTRAL databases up to March 2022. The epidemiological validity and methodological quality of the evidence were graded based on commonly accepted criteria.
Results
Twenty-nine meta-analysis publications were identified (41 individual meta-analyses, 33 risk factors, 242 primary study comparisons). Assessed risk factors included nutritional exposures, disease entities (gastrointestinal, endocrinological, dermatological, other systems), infections, biomarkers, and lifestyle characteristics. Of the 41 meta-analyses, 2 (5%) were graded as of high validity evidence to support the association with higher osteoporosis risk (hyponatremia, peptic ulcer), and 4 (10%) as of moderate validity (lower total dairy or fruit intake, Parkinson's disease, higher urine cadmium). Of the 29 meta-analyses, 2 (7%) were judged as of high quality (fruit intake, atopic dermatitis). Most meta-analyses evaluated as of high/moderate validity or high quality included a few primary longitudinal studies.
Conclusion
Despite the breadth of the meta-analytical literature on osteoporosis risk factors, only hyponatremia, peptic ulcer, lower total dairy or fruit intake, Parkinson's disease, and higher urine cadmium were evaluated as of high/moderate validity. Identifying epidemiologically robust risk factors could help guide clinical practice and public health policy.

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P571

Usefulness of 18F-Fluorocholine Positron Emission Tomography–Computed Tomography in locating parathyroid adenomas in primary hyperparathyroidism

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Background
Parathyroidectomy is the only definitive treatment for primary hyperparathyroidism (PHPT). Identifying parathyroid adenomas (PA) before surgery is essential to perform minimally invasive surgery and to achieve higher cure rates.
Methods
Retrospective study of patients with PHTP who underwent 18F-Fluorocholine Positron Emission Tomography- Computed Tomography (18FCH-PET-CT) between 2019 and 2021 at our center due to non-localization of PA or discrepancy in previous imaging studies. Diagnostic accuracy of 18FCH-PET-CT and its concordance with other studies and the gold-standard (surgical location) were evaluated.

Results
86 patients with 18FCH-PET-CT, 99mcTc methoxyisobutylisonitrile scintigraphy (MIBI) and ultrasound (US) were included for analysis.18FCH-PET-CT was positive in 53 patients(61.6%) and negative or inconclusive in 33(38.4%). Group with positive 18FCH-PET-CT($n=53$): 77.3% female; 60 mean age. 86% hypercalcemia, 26.4% lithiasis; 37.1% osteoporosis. Mean serum calcium 11 mg/dl; median PTH 125 pg/ml and mean VitD 29.7 ng/ml. In this group, 28 patients underwent surgery and 25 are on the surgery waiting list (SWL). 18FC-PET-CT 100% match the surgical location allowing minimally invasive surgery in 18 out of 28 patients(64.2%). 5 PA were only located with 18FCH-PET-CT. These PA were smaller, with lower mean serum calcium and lower median PTH than those also located by US and/or MIBI. 9 PA were located with US but not with MIBI; and 5 with MIBI but not with US; in both subgroups localization matched with 18FCH-PET-CT and surgery. There were 6 discordant cases between US and MIBI, 1 US and 5 MIBI matched 18FCH-PET-CT and surgery. In 3 cases the PA was located with MIBI and US therefore 18FCH-PET-CT was not needed. Patients on SWL with positive 18FCH-PET-CT($n=25$). 11 PA were only located with 18FCH-PET. 6 PA were located with US but not with MIBI; and 2 with MIBI but not with US; in both subgroups localization matched with 18FCH-PET-CT. There were 6 cases discordant between US and MIBI, 3 US and 3 MIBI matched 18FCH-PET-CT. Group with negative 18FCH-PET-CT($n=33$): 69.6% female; 57 mean age. 48% hypercalcemia, 33% lithiasis; 48% osteoporosis. Mean serum calcium 10.3 mg/dl; median PTH 112 pg/ml and mean VitD 35 ng/ml. In this group in 22 patients US and MIBI were also negative.
Conclusions
18FCH-PET-CT was superior to US and MIBI locating PA, allowing us to perform minimally invasive surgery on our patients. PA identified only with 18FCH-PET-CT were smaller, with lower mean serum calcium and lower median PTH than those also located by US and/or MIBI.

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P572

Similarities and differences between thyroid and parathyroid nodules on ultrasound: the PARATH-US study

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Context
Cervical ultrasound is a frequently used and an accessible operator-dependent tool, which contributes to the characterization of thyroid nodules and to the preoperative localization of pathological parathyroid glands. However, thyroid nodules may be confused with parathyroid lesions. There is no study directly comparing thyroid and parathyroid nodules on ultrasound.
Objectives
1) To describe the ultrasonographic characteristics of parathyroid lesions and to establish bio-radiological correlations; 2) to identify specific features differentiating them from thyroid nodules, by using the EU-Tirads ultrasound stratification scoring risk.
Patients/Methods
PARATH-US is a single-center study. We included 160 parathyroid lesions proved biologically (through intranodular PTH measurement) or histopathologically after surgical excision and compared them with 169 age, sex and maximal diameter-matched thyroid nodules in patients undergoing ultrasound examination in the Endocrinology Department of Bicêtre Hospital from 2016 to 2022.
Results
160 parathyroid lesions belonging to 141 patients (53.8 ± 18.5 years, 104 women, serum calcium levels 2.94 ± 0.33 mmol/l, PTH levels 377.9 ± 614.6 ng/l) were included. 66.4% of them were adenomas, 27.6% hyperplasias, 4.3% atypical adenomas. The maximal diameter of parathyroid lesions was 14.3 ± 7.5 mm, their volume 0.89 ± 2.18 ml. 62.7% of the lesions were solid, 85.4% were separated from the thyroid parenchyma by a hyperechoic septum and 56.7% had intranodular vascular spot. Parathyroid hyperplasias were smaller (0.57 ± 0.76 vs 1.31 ± 2.74 cm3, $P=0.037$) and had less vascular spots (26% vs 73.5% $P=0.004$) than adenomas. In patients harboring a unique parathyroid lesion, strong positive correlations were found between serum calcium, PTH levels and lesion diameter/volume (r>0.58 and $P<0.001$ for all comparisons). Parathyroid lesions more frequently presented an anterior hyperechoic septum than thyroid nodules (85.4 vs. 5.2%, $P<0.0001$, positive predictive value (PPV) set at 99% [95% CI 97-100]). Parathyroid lesions presented with various morphologies, and had more often a non-oval shape than thyroid nodules (55.8 vs. 17.4%, $P<0.0001$, PPV 82% [75-87]). Marked hypoechogenicity (EU-Tirads 5) was found more often within parathyroid lesions (41.2%) than thyroid nodules (18.9%, $P<0.01$, PPV 67% [59-74]). Conversely, the prevalence of kystic content was found more frequently in thyroid than in parathyroid nodules (12,4% vs. 3,6%, $P=0.0037$).
Conclusion
We describe the ultrasound characteristics of a large series of parathyroid adenomas/hyperplasias. We show that parathyroid lesions present high-risk ultrasound features, if confused with thyroid nodules. We demonstrate the presence of specific morphological ultrasound characteristics, which help differentiating parathyroid from thyroid lesions

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Evaluation Of Progranulin Expression in Parathyroid Adenomas and Its Relationship with Clinical Parameters

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Introduction
Primary hyperparathyroidism (PHPT) clinic occurs when the parathyroid glands secrete excess parathormone (PTH) due to hyperplasia, adenomatous or carcinomatous change. In the pathogenesis of the disease, dysregulation has been observed in extracellular signal-regulated 1/2 (ERK 1/2) pathways from the mitogen activated protein kinase (MAPK) family, c-Jun N-terminal kinase (JNK) pathways, and phosphatidylinositol-3 kinase (PI3K) pathways. Progranulin (PGRN) is a glycoprotein found in many tissues in the body, activation of MAPK, JNK and PI3K pathways by PGRN has been observed in studies. Based on these shared pathways, PGRN expression in parathyroid adenomas and its clinical effects were investigated.
Methods
182 cases were included in our study, consisting of 102 PHPT patients who were operated on with adenomas and 80 cases in the control group. The biochemical and clinical data was evaluated. Anti-GRN antibody was applied at 1/300 dilution to the parathyroid samples and statistical analysis was performed. Tissues without staining were considered negative, staining between 1% and 25% were considered weak positive and tissues with staining above 25% were considered strong positive.
Results
While the mean age of the patients was 59.63 ± 12.15 years, the mean age of the control group was 57.01 ± 12.47 years. 91 of 102 patients were female and 11 were male; in the control group 67 were female and 13 were male. No statistical significance was found in terms of age and gender distribution ($P=0.156$, $P=0.378$). Of 102 patients, staining with anti-GRN was negative in 59, mild in 26 and strong in 17. All samples in the control group showed strong staining. PGRN expression was significantly lower in the patient group ($P<0.001$). Staining scores were compared with biochemical and clinical parameters, no significant difference was found ($P>0.05$). The mean calcium levels in the patient and control group were 11.33 ± 0.9 and 9.31 ± 0.45 mg/dl respectively. The mean PTH in the patient group was 173.80 ± 95.35 pg/ml. Biochemical and clinical parameters were compared in the patient group, positive correlation was found with calcium and PTH levels ($P<0.001$); phosphorus and forearm bone density were negatively correlated with PTH levels ($r=-0.38$, $P<0.001$; $r=-0.32$ $P=0.015$). Calcium and phosphorus levels were also negatively correlated ($r=-0.40$ $P<0.001$).
Conclusion
We found that PGRN expression was significantly decreased in sporadic parathyroid adenomas compared to the control group. PGRN may be an important factor in pathogenesis of parathyroid adenomas, more comprehensive studies are needed to investigate the clinical associations and examine the underlying molecular pathways.

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P574

A long and challenging journey from the first non-typical gastrointestinal manifestations to the diagnosis of primary hyperparathyroidism and MEN 1

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Introduction
Primary hyperparathyroidism (PHPT), as a state of chronic hypercalcemia, can be manifested by non-typical symptoms which can delay the proper diagnosis for many years and lead to serious preventable complications affecting the patient's quality of life.
Case report
A 52-year-old woman with hypertension, thyroid nodular goiter treated with radioactive iodine and a 20-year history of gastric and duodenal ulcerative disease, complicated by gastric perforation in 2002 and bleeding from duodenal ulcers in 2019, was admitted to the hospital in January 2020 due to general and muscle weakness and ongoing diarrhea for many years resolving only after PPI treatment, which made her incapable of working. Laboratory tests revealed serum concentrations of calcium 3.04 mmol/l (2.10-2.55), phosphate 0.68 mmol/l (0.74–1.52), urinary calcium 14.76 mmol/24 h (2.50-7.50), serum concentrations of PTH 282.8 pg/ml (15.0-68.3), alkaline phosphatase 120 IU/l (37-123). Other relevant laboratory findings were: serum concentrations of gastrin 735 ng/l (13-115) and chromogranin A 1597.67 ng/ml (<100), and normal renal and thyroid function. Neck ultrasound showed a hypoechoic, marginal vascularized lesion 7x6x10mm behind the right thyroid lobe. In a further step, fine needle aspiration and 99 Tc-sestamibi scan were performed, confirming the presence of a single parathyroid adenoma in this location. Moreover, a compression fracture of the L2 vertebra (asymptomatic) and bilateral adrenal tumors, but no renal stones or pancreatic lesion, were detected in abdominal CT. Osteoporosis was confirmed in DEXA. Somatostatin receptor scintigraphy (SRS) did not detect any abnormalities. After excluding pheochromocytoma, the patient underwent parathyroidectomy. However, after surgical treatment, persistent hypercalcemia (2.71mmol/l) and elevated PTH level (378.9 pg/ml) were observed. Conventional imaging, such as neck CT and MRI, 99 Tc-sestamibi scan did not show the localization of the lesion. The diagnostics was extended by performing 18F-fluorocholine PET/CT and revealed hyperfunctioning parathyroid tissue of 8mm in size, between the C7 vertebra and the esophagus. The patient required reoperation, which was followed by the development of hypoparathyroidism, although the peptic ulcer disease and persistent diarrhea resolved spontaneously. Considering the presence of bilateral adrenal tumors, multiple parathyroid adenomas and PPI-dependent diarrhea, a genetic test was performed, confirming multiple endocrine neoplasia type 1 (MEN 1).
Conclusions
The presented case shows how difficult and long the process from first symptoms to proper diagnosis could be. Recurrent peptic ulcers should always prompt to look for secondary causes, especially PHPT.

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P575

Cardiac MRI revealed altered structural and functional myocardium in patients with primary hyperparathyroidism: preliminary results

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Aim
The primary objective of this study was to evaluate the structural and functional cardiac parameters with MRI in patients with primary hyperparathyroidism (pHPT) before and after successful surgery.
Method
In this prospective study 16 patients with pHPT were included. Detailed cardiac magnetic resonance imaging (MRI) examinations were performed preoperatively and at six months post-surgery. Following parameters were measured: Left ventricle ejection fraction (LVEF), left ventricle end-diastolic volume (LVED), left ventricle stroke volume and left ventricle stroke index; left ventricle cardiac output and cardiac index; left ventricle end-diastolic wall mass, left ventricle peak filling rate and peak filling time; E and A, mitral deceleration time, left atrium volume index (LAVI). In addition, pre-contrast T1-T2 relaxation times and ECV values were analyzed.
Results
The mean $\pm$SD age of the 16 patients was 54 $\pm$ 12 years. The majority of the patients were female (F/M: 11/5). Only two patients had symptomatic pHPT, rest were asymptomatic. Evaluation of the asymptomatic patients revealed nephrolithiasis in four (26%) and osteoporosis in six (46%). All of the patients had sporadic disease. The mean $\pm$SD levels of PTH and calcium were 170 $\pm$ 84 pg/ml and 11.2 $\pm$ 0.5 mg/dl, respectively before surgery. The culprit lesion was adenoma in 15 (93%) and hyperplasia and adenoma could not be differentiated in one. After successful surgery PTH and calcium were decreased: 64 $\pm$ 28 pg/ml and 9.7 $\pm$ 0.2 mg/dl, respectively. Comparative cardiac MR images demonstrated lower apical global ECV values postoperatively. Apical global ECV values decreased from 27.9 $\pm$ 3.6% to 26.4 $\pm$ 2.6%, (P =0.015). The both atrial (late ventricular filling velocities from 43.80 $\pm$ 12.97 cm/s to 37.10$\pm$ 11.89 cm/s, P=0.047) and ventricular (left ventricular ejection fraction from 62.81 $\pm$ 3.74% to 60.31 $\pm$ 4.65%, P=0.021; early ventricular filling velocities from 43.78 $\pm$ 9.25 cm/s to 36.10 $\pm$ 9.57 cm/s, P=0.017) systolic forces of the heart were reduced after the control of PTH secretion. There were no differences in other MRI parameters.
Conclusion
In this first study that evaluates structural and functional cardiac MRI parameters in a cohort of patients with pHPT (especially in asymptomatic patients) we showed that apical ECV values, which is an indicator of myocardial fibrosis, were improved after successful surgery. Moreover, we determined that myocardium contracts stronger in primary hyperparathyroidism.

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P576

Hypercalcitoninemia in a large cohort of adult and paediatric patients with PTH-resistance syndromes

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Inactivating PTH/PTHrP signaling disorders (iPPSDs, historically named pseudohypoparathyroidism (PHP)) are a group of rare disorders associated with resistance to parathormone (PTH) and other hormones due to impaired hormonal signaling via G protein coupled receptors. Hypercalcitoninemia has been reported in these patients, however very few reports are available. The aim of this study was to further investigate the prevalence and characteristics of hypercalcitoninemia in both paediatric and adult iPPSD patients. We retrospectively collected data from two cohorts of iPPSD patients, both in regular follow-up at two European Endocrinology tertiary centres. The first cohort included 88 paediatric patients with available calcitonin (CT) measurements, and the second consisted of 43 adult patients with at least one simultaneous measurement of CT and PTH. In the latter cohort, c-cell function was assessed by calcium stimulation test in 19 patients. In the paediatric cohort 65.9% had hypercalcitoninemia with mean basal CT levels of 24.9$\pm$26.8 ng/l, 12.1% developed hypercalcitoninemia before the age of 2 and 65.5% before the age of 10. In the adult cohort, 53.5% had hypercalcitoninemia with mean CT levels of 21.6$\pm$8.3 ng/l. Calcitonin measurements remained stable throughout a mean follow-up time of 59$\pm$47.3 months. No correlations were detected between CT levels and PTH levels (P=0.5). Other etiologies of hypercalcitoninemia were excluded, i.e. renal failure and drug interferences, and all patients underwent regular thyroid ultrasound to screen for medullary thyroid cancer (MTC). We also performed calcium stimulation test in 19 patients and we compared CT levels with a control group of 33 healthy patients and a group of 20 patients with pathological evidence of MTC or c-cell hyperplasia (MTC-CCH). We found that there was a statistically significant difference in both basal (P=0.034) and stimulated (P=0.002) CT levels in control and iPPSD groups, as well as control and MTC-CCH group (basal CT levels P=0.000; stimulated CT levels P=0.000), on the contrary there was no significant difference in both values in iPPSD and MTC-CCH group. Our study confirms that elevated calcitonin levels are commonly found in both adult and paediatric patients with PTH-resistance syndromes. Our findings suggest that it may be a condition that develops in early age and remains stable throughout time. Moreover, these patients show an hyperresponsiveness to calcitonin stimulation test. Differential diagnosis with MTC based on CT levels, both basal and stimulated, can be challenging.

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P577

Trabecular bone score increases the proportion of patients with asymptomatic primary hyperparathyroidism meeting surgical criteria

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Context
Several studies have shown that Trabecular Bone Score (TBS) predicts fractures independently of Bone Mineral Density (BMD) measured with Dual Energy X-ray Absorptiometry (DXA), even in patients with Primary Hyperparathyroidism (PHPT), known to have deteriorated bone microarchitecture. Low TBS values alone are still not considered as a single criterium to recommend parathyroid surgery. Measuring bone quality in patients with PHPT may be helpful to identify a proportion of patients at increased fracture risk regardless of the other known criteria used to recommend parathyroidectomy.
Objective
To describe the prevalence of low bone quality measured by TBS in a cohort of patients diagnosed with PHPT to evaluate its impact on the clinical management of PHPT.
Design
Cross-sectional, observational.
Setting
Academic.
Patients
From February 2021 to January 2023, 133 patients with asymptomatic classical PHPT (i.e. with elevated total, albumin adjusted, or ionized serum calcium) were consecutively evaluated. All patients underwent complete serum and urinary assessment in the same laboratory, bone density test with TBS by using the same DXA machine, and renal ultrasound to screen for nephrolithiasis or nephrocalcinosis. We selected 119 patients who had a DXA performed at all 3 sites along with TBS. We retrospectively applied to each patient the recently revised criteria for parathyroid surgery as per the V International Workshop.
Main outcome measures
TBS, BMD, and biochemistries. TBS <1.200 was used to discriminate low bone quality.
Results
Mean age of the patients was 67 ± 12 years and most were women (102/119, 85.7%). TBS was low in 34/119 patients (28.6%) with PHPT. Patients met the criteria for parathyroid surgery respectively due to hypercalcemia (>1 mg/dl above the upper normal limit) (16/119, 13.4%), hypercalciuria (>250mg/day for females or > 300mg/day for males) (53/119, 44.5%), any previous clinical fragility fracture or morphometric vertebral fracture (28/119, 23.5%), reduced GFR (<60ml/min) (19/119, 15.9%), age less than 50 years (8/119, 6.7%), nephrolithiasis (20/119, 16.8%). Among the 29 patients not meeting any surgical criteria, 3 (10.3%) had low TBS. Among those with BMD T-score above -2.5 at all three sites, TBS was reduced in 6/48 (12.5%) patients. Lower TBS was associated with increasing age and lower BMD T-scores, with a strong association with osteoporosis at 1/3 distal radius (Odds-Ratio: 3.98, $P=0.001$).
Conclusions
By implementing routine TBS measurement, an estimated additional 10% of patients, who would otherwise not meet the current listed surgical recommendations, could benefit from curative parathyroid surgery to reduce fracture risk.

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Assessment of dxa derived bone geometry parameters in early breast cancer patients: a cross-sectional study

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Introduction
Bone mineral density (BMD) is considered a valid surrogate of bone strength in postmenopausal women, however it lacks sensitivity in individual fracture risk assessment in the setting of women with early breast cancer (EBC) patients treated with aromatase inhibitors (AIs). Indeed, mechanical resistance of bone only partially depends on bone quantity, and bone geometry and size play an important role in bone resistance to fractures. In this cross-sectional study, we assessed for the first time the association between vertebral fractures (VFs) and parameters of bone geometry in women with EBC patients treated with AIs. Moreover, we aimed also to provide a preliminary information on the possible effects of anti-resorptive drugs on bone geometry parameters.
Methods
HR-positive EBC postmenopausal women who were candidates to AIs therapy, with normal renal function, without any bone metabolic disorders, and no previous or current treatment with anti-osteoporotic drugs or glucocorticoids. Were consecutively evaluated for bone strain index (BSI), dual-X-ray absorptiometry (DXA) based parameters of bone geometry and morphometric VFs. Subjects were categorized in 3 groups in order to evaluate the impact of AIs and denosumab on bone geometry: AI-naive, AI-treated minus (AIDen-) or plus (AIDen+) denosumab.
Results
A total of 610 EBC patients entered the study: 305 were AI-naive, 187 AIDen-, and 118 AIDen+. In the AI-naive group, fractured patients compared to non-fractured ones presented a lower total hip BMD (mean 0.77 vs 0.84, $P=0.001$) and T-score (1.38 vs 0.86, $P=0.001$), but higher femoral BSI (femoral neck BSI 1.93 vs 1.70, $P=0.001$). Concerning bone geometry parameters, AI-naive fractured patients reported a significant increase in femoral narrow neck (NN) ($P=0.037$) endocortical width ($P=0.035$), femoral NN subperiosteal width ($P=0.045$), intertrochanteric buckling ratio (BR) ($P=0.007$), femoral shaft (FS) BR ($P=0.007$) and endocortical width ($P=0.035$), as compared to non-fractured patients. Some of these associations were maintained also in AI-treated women. Specifically, AIDen-fractured patients showed higher values of BR ($P=0.014$), lower cortical thickness ($P=0.033$) and higher FS endocortical width ($P=0.019$) as compared to non-fractured subjects. Conversely, CSA and CSMI in both IT area and FS area were significantly decreased according to the presence of VFs in the AIDen+ population.
Conclusion
This study suggests how DXA-derived bone geometry parameters can be variably associated with VFs in EBC patients, either AI-naive or AI treated in combination with denosumab. This finding reflects the need of a tailored choice of fracture risk parameters in the 3 subgroups of EBC patients.

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P579

Hyperglycemia-induced unique transcriptional changes in osteocytes

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Introduction
Diabetes leads to skeletal fragility and an increased fracture risk. As a master regulator of bone-remodeling, osteocyte dysfunction may play a role in the pathogenesis of diabetes-related skeletal fragility. To study the effects of hyperglycemia on the osteocyte in-isolation, we used the osteocyte-like cell line IDG-SW3 taking an unbiased multi-omics-based approach.
Methods
IDG-SW3 cells were plated in a differentiation osteogenic medium under 3-conditions: normal glucose (5mM; NG), high-glucose (25mM; HG) and mannitol 20mM with glucose 5mM to control for the hyperosmolarity induced by HG. Media was changed twice weekly for 28 days, with cells harvested at 1,3,7,14, 21 and 28-days post differentiation induction. 3-biological-replicates were used for each condition with the entire experiment repeated 3-times. RNA was extracted from cell lysates 14 days after induction to osteogenesis with bulk RNA-SEQ performed. Protein was extracted at day 16 after induction to osteogenesis with proteomics analysis by LCMS.
Results
HG conditions led to lower PH in the supernatant and a delay in markers of osteocyte differentiation. RNA-SEQ analysis revealed 1340 differently expressed genes (767 up 573 down; DEGs). Interestingly, mannitol led to a much smaller transcriptional change with only 103 DEGS vs NG (cut-off of FC>2 and p.adj <0.05) with just 38 DEGs in common between the comparisons. Ingenuity Pathway Anaylsis (IPA) of DEGs (HG vs NG) revealed significant deactivation of the autophagy related pathways CLEAR Signaling (Z-score -3.015, -log[B-H *P*-value] 8.31) and Phagosome Formation (Z-score -3.43, -log[B-H *P*-value] 1.458); a pattern not observed in mannitol vs NG. Proteomics analysis revealed HG led to activation of the senescence pathway (Z-score 1.213 -log[B-H *P*-value] 3.66) and deactivation of the CLEAR signaling pathway

score -0.755 -log[B-H *P*-value] 3.03). **Conclusion:** These results reveal the differential effects of hyperosmolarity and hyperglycemia on transcriptional changes and cell differentiation in the osteocyte, which may play a role in the pathophysiology of diabetes-related skeletal fragility. Specifically, the deactivation of autophagy and activation of senescence pathways induced by hyperglycemia in osteocytes warrant future research, as they may serve potential therapeutic targets for prevention and treatment of diabetes-related skeletal fragility.

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P580

Low trabecular bone score better predicts prevalent vertebral fractures in younger rather than older women starting endocrine therapy for breast cancer

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Context
Although Trabecular Bone Score (TBS) has been widely and independently associated with fragility fractures, its diagnostic power in certain populations remains to be established. Women initiating aromatase inhibitors for breast cancer should be screened for bone health to prevent cancer treatment-induced bone loss as much as possible. TBS is regarded as an adjunctive tool to evaluate these patients, but thresholds of pharmacologic interventions are still a gray zone, especially in younger women.
Objective
To test the diagnostic power of TBS to predict prevalent vertebral fractures at the start of endocrine therapy for breast cancer. Low TBS was defined as <1.2.
Design
Cross-sectional, real-life.
Setting
University hospital.
Patients
We retrospectively evaluated 223 consecutive ambulatory women with newly diagnosed early breast cancer from February 2021 to November 2022. They all underwent a prespecified protocol which included mineral biochemistries with bone turnover markers, bone mineral density with TBS, and endocrine consultation. Lateral X-rays images of the spine performed just before breast surgery were reviewed to screen for asymptomatic vertebral fractures.
Results
Mean age of the patients was 61 ± 12 years. Overall, 65 patients (29%) had normal bone density (BMD), 90 patients (40%) had osteopenia, and 68 patients had osteoporosis (31%), with 35/223 (15.7%) women having low TBS. The prevalence of low TBS progressively increased with decreasing BMD (6.2% in normal BMD, 10% with osteopenia, and 32.3% with osteoporosis; $P<0.001$). Vertebral fracture prevalence was 24/223 (10.8%). BMD category was highly associated with prevalent vertebral fractures ($P<0.001$), but this was not the case for low TBS alone ($P=0.597$). A low TBS highly correlated with advanced age ($P<0.001$), independent of other clinical or biochemical parameters (age, BMD T-score, renal function, 25-OH vitamin D, PTH). ROC analyses showed that TBS Area Under Curve (AUC) was 0.647 ($P=0.021$), comparable ($P=0.561$) to that of femur neck T-score (AUC $=0.688$, $P=0.003$) for detecting prevalent vertebral fractures. Notably, the diagnostic power of TBS was much higher in women younger than 65 years, with TBS AUC being 0.769 ($P=0.032$), with femur neck BMD being much less accurate (AUC 0.564, $P=0.339$). By contrast, TBS AUC dropped to 0.484 ($P=$NS) in older women, whereas femur neck T-score retained its expected diagnostic accuracy (AUC 0.690, $P=0.008$).
Conclusions
TBS rather than BMD could better predict prevalent vertebral fractures in women younger than 65 initiating aromatase inhibitors, as compared to older women. In the latter group, femur neck BMD T-score was confirmed to be more accurate.

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P581

Association Between Primary Hyperparathyroidism and Cardiovascular Outcomes: A Systematic Review and Meta-analysis

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Background
Parathyroid hormone excess is associated with increased risk of cardiovascular disease (CVD). The aim of the study is to evaluate the correlation between primary hyperparathyroidism (PHPT) and CVD or cardiovascular death (CV death).
Method
Database research was conducted via PubMed and Embase on November 21st, 2022, with key words as following: "cardiovascular disease" "cardiovascular death" and "primary hyperparathyroidism". A total of 10 cohort studies and 1 randomized controlled trial were included in our analysis. Our primary outcomes were CV death and CVD. Patients with PHPT were compared to general population. We also compare patients that had received parathyroidectomy (PTX) to those without PTX. The variables were pooled as hazard ratios or standard mortality ratios, and a meta-analysis using random-effects model was performed.
Result
A total of 11 studies were identified, including 259,218 PHPT patients with or without PTX, and of which 192,315 were women (74.1%). The average of mean ages reported in 9 studies available was 61.9 years. PHPT was associated with higher risk of CV death when compared to general population (RR 1.61 [95% confidence interval (CI) 1.47-1.78]); however, there was no significant difference of CVD risk between patients with PHPT and general population (RR 1.73 [95% CI 0.87-3.47]. When compared to patients without PTX, PTX had lower risk of CV death (RR 0.75 [95% CI 0.71-0.80]) and CVD (RR 0.92 [95% CI 0.90-0.94]).
Conclusions
Patients with PHPT had higher risk of CV death than general population, and PTX reduced the risk of CV death and CVD.

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P582

Effectiveness of Jugular Venous Sampling of Parathormone in Imaging Negative Patients with Primary Hyperparathyroidism

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Introduction
The only curative treatment of primary hyperparathyroidism (pHPT) is surgery. Accurate pre-operative localization of abnormal parathyroid glands is an essential prerequisite to reduce the complication risk associated with surgery. We aimed to determine the diagnostic value of jugular venous sampling (JVS) in cases of pHPT in which the location of parathyroid adenomas could not be determined through various preoperative imaging studies.
Methods
A retrospective study was conducted with 22 patients with pHPT who underwent bilateral JVS. The samples were collected from the most inferior portion of each internal jugular vein and sent for standart PTH measurement. $>10\%$ gradient difference between the sides was accepted as positive. The patients' laboratory results, preoperative ultrasonography (US) and parathyroid scintigraphy findings, JVS results, and postoperative pathology results were recorded.
Results
JVS was performed in 22 patients (1 M/21 F) with pHPT. 15 of the patients had negative ultrasound and scintigraphy findings. Gradient differences were found in a total of 12 patients (54%), 9 on the right and 3 on the left. Gradient difference was found in JVS in 6 patients with negative scintigraphy and in 5 patients with negative US findings. Although 4 of them were positive in ultrasound and 3 of them were positive in scintigraphy, no gradient difference was found in JVS. Among 12 patients, the JVS gradient localization was found to be incompatible with surgical exploration in only one patient. All patients' pathology results were reported as parathyroid adenoma.

Discussion
In cases with small or multiple parathyroid lesions, the location of lesions cannot be determined using US and ^{99m}Tc-sestamibi SPECT. JVS is generally recommended to lateralize the lesion in scintigraphy-negative patients undergoing primary surgery. Alvarado *et al.* found a 56% positive lateralization in a study with both positive and negative pHPT patients, and a positive lateralization of 76% in the control group without parathyroid disease. The authors reported that JVS was not sufficient to determine the location of imaging negative parathyroid adenomas. On the otherhand, Denise *et al.* found that JVS was correct in in localization the side of the abnormal gland in 81% of the patients with pHPT.
Conclusions
JVS may be used as an adjunctive technique for preoperative localization of parathyroid lesions that cannot be located by non-invasive imaging studies if a gradient difference is reached and more extensive studies are needed to confirm the role of this tecnique before surgery.

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P583

Impact of Zoledronate or Denosumab on Bone-related Biochemical Parameters in Osteoporotic Postmenopausal Women with Primary Hyperparathyroidism

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Introduction
Antiresorptive treatment can preserve bone mineral density (BMD) in patients with primary hyperparathyroidism (PHPT) when surgery is not feasible or desired. We aimed to compare the impact of zoledronate vs denosumab on bone-related biochemical parameters in this population.
Methods
We analyzed preliminary data from our ongoing randomized trial on osteoporotic postmenopausal women with PHPT who are being treated either with zoledronate 5 mg iv once a year (ZOL group) or with denosumab 60 mg sc every six months (DMAB group) (ClinicalTrials.gov Identifier NCT04085419). Here we compare their laboratory parameters and bone turnover markers at baseline and three months after starting the treatment.
Results
We studied 21 osteoporotic females (with mean BMD at LS 0.841 (SD 0.132), TH 0.749 (0.117), FN 0.645 (0.084), 1/3R 0.500 (0.066) g/cm^2) aged 76.2 (7.1) years and 26.9 (9.7) years from menopause with BMI 28.78 (4.4) kg/m^2. Eight patients received zoledronate (ZOL), and thirteen were treated with denosumab (DMAB). There were no statistically significant differences in baseline characteristics between the two groups. Three months (3M) after starting treatment, there was a statistically significant fall in serum calcium (S-Ca) levels in the ZOL group only (baseline S-Ca 2.7 mmol/l (0.1) vs. 3M S-Ca 2.6 mmol/l (0.1); $P=0.033$). Intact parathyroid hormone (iPTH) values increased in both groups; the increase did not differ between the two groups (ZOL Δ iPTH 44.28 (113.54) vs. DMAB Δ iPHT 42.84 (63.33); $P=0.9$). Baseline 25 OH vitamin D was similar in both groups, with the average value 56.8 (18.8) nmol/l, and remained unchanged after treatment. Bone turnover markers decreased statistically significantly in both groups (ZOL CTX baseline 0.495 (0.3) vs. 3M 0.098 (0.12) μg/l; $P<0.01$; ZOL P1NP baseline 74.5 (28.3) vs. 3M 19.9 (9.9) μg/l; $P<0.01$; DMAB CTX baseline 0.89 (0.77) vs. 3M 0.01 (0.01) μg/l; $P<0.01$; DMAB P1NP baseline 79.7 (34.4) vs. 3M 14.05 (4.9) μg/l; $P<0.01$). The differences between the groups were not statistically significant (ZOL Δ CTX 0.4 (0.3) vs. DMAB Δ CTX 0.88 (0.77) μg/l; $P=0.1$ and ZOL Δ P1NP 54.55 (24.86) vs. DMAB Δ P1NP 65.65 (32.08) μg/l; $P=0.4$).
Conclusion
Preliminary analysis showed a significant decline in calcium levels only in the ZOL group. Bone turnover markers significantly decreased in both groups—the apparent numerical difference in decrease after ZOL vs after DMAB was not statistically significant.

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P584

Three Times Unlucky-Severe Hypercalcaemia of Immobility Compounded by Undiagnosed Hyperthyroidism and Milk Alkali Syndrome

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Background
Immobility can be associated with severe hypercalcaemia, especially when compounded by other risk factors such as concurrent hyperthyroidism and high dietary calcium/milk intake and associated complications such as renal stones and fractures.
Clinical case
59y female presented acutely with confusion, vomiting, constipation and muscle weakness. She had history of obesity, stable Crohn's disease with no recent increase in colonostomy output. Her calcium was high at 4 mmol/l (n-2.2-2.6 mmol/l), PTH low, but not suppressed at 2 pmol/l (n- 1.8-6.8 pmol/l), ALP- 138 U/l (n- 30-130 U/l), bicarbonate- 27.3 mmol/l, pH- 7.375. Screen for myeloma, sarcoid and cancer was negative. FT4 raised at 19 pmol/l (n- 7.7-15.1 pmol/l) and TSH 0.01 mu/l (n- 0.34-5.6 mu/l). CT scan excluded cancer and identified stones in kidneys and bladder and healed pubic ramus fractures suggesting a more insidious onset. She had moderate goitre. No history of lithium, calcium supplements, antacids use. Three months prior to presentation had cCa- 2.78 mmol/l, but not investigated. Dietary enquiry revealed consumption of minimum of 2-3 pints (1.1-1.7l) of semi-skimmed milk per day alongside at least two yogurts and cheddar cheese. This intake was calculated to be at least 1910-1614 mg/daily of calcium [2-3 x 704 mgs of calcium (milk) + 2 x 140 mg (yoghurts) + 222 mg (30g of cheddar cheese)]. Social enquiry revealed she has been completely bedbound for eight months due to severe knee osteoarthritis and malunion ulna fracture and chronic elbow dislocation impacting her ability to use walking aids. Patient responded to IV hydration and pamidronate infusion. Treatment with carbimazole was commenced and reduced calcium intake was advised. She was referred for urgent ulna reunion surgery followed by knee surgery. Her calcium reduced to 2.86 mmol/l and subsequently to 2.68 mmol/l during follow up. Her thyroid function normalised.
Conclusion
Our patient had hypercalcaemia of immobility, hyperthyroidism and milk alkali syndrome. It is important to be aware of these rarer causes (even in patients not obviously suffering paralysis from a spinal cord injury or a stroke) when alternative diagnoses have been excluded and explore them in detail at presentation. Immobilisation affects balance between bone formation and resorption by increased sclerostin secretion by osteocytes, which diminishes the bone formation stimuli by blocking the Wnt-Runx2 pathway in the osteoblast. This was paired with increased bone turn over from hyperthyroidism, oral calcium load and diminished renal calcium excretion from milk alkali syndrome.

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P585

Evidence of a non-classical phenotype of hypoparathyroidism in a cohort of adult patients with iron overload diseases

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Background
Iron overload disorders (IOD) are associated with a higher occurrence of unbalanced calcium (Ca)-phosphorous (P) metabolism, including hypoparathyroidism (HPT). However, data about prevalence and presentation of HPT in this setting are scanty. A Ca/P ratio <2.32 has been proposed to detect HPT in the general population.
Aim
To characterize Ca-P homeostasis, particularly the prevalence of HPT, in a cohort of adult patients with IOD compared to healthy subjects. Furthermore, the performance of Ca/P ratio in identifying concealed forms of HPT in IOD patients was tested.
Methods
A single-center, cross-sectional, case-control study was carried out including 58 IOD patients (39 patients with β-thalassemia (β-T) and 19 patients with hereditary hemochromatosis (HH)) and 76 controls. The main outcomes were: serum Ca, P, Ca/P ratio and intact parathyroid hormone (PTH). Primary hypoparathyroidism (pHPT) was defined as hypocalcemia with low/inappropriately normal PTH, whereas subclinical hypoparathyroidism (sHPT) as serum Ca at the lower limit of normal range with low PTH.
Results
IOD patients had lower serum Ca ($P=0.032$), higher serum P ($P=0.004$) and lower Ca/P ratio ($P<0.001$) compared to controls, whereas no difference was found for serum PTH. Patients with β-T had higher serum P ($P<0.001$), lower Ca/P ratio ($P<0.001$) and lower serum PTH ($P<0.001$) compared to patients with HH and

controls, whereas no difference was found for serum Ca among subgroups. On the other hand, Ca/P did not significantly differ comparing HH and controls. pHPT was found in 6 patients with β-T (15.4%) and in none patients with HH; sHPT was found in 19 patients with β-T (48.7%) and in 1 patient with HH (5.3%). IOD patients with HPT showed lower Ca/P ratio ($P<0.001$) compared to IOD patients without HPT. A Ca/P ratio <2.32 allowed the correct identification of 19 out of the 26 IOD patients with overt or sub-clinical HPT (sensitivity 73.1%; specificity 87.5%). IOD patients with Ca/P ratio <2.32 had an almost 20-fold increased likelihood to be affected by HPT (OR 19.0 [4.9-74.0]; $P<0.001$).

Conclusions

Despite a low prevalence of overt pHPT, the non-classical phenotype sHPT seems to be a common finding in IOD patients. The Ca/P is useful to detect HPT even in this context. A periodic evaluation of serum Ca and P should be included in the follow-up of these patients to early detect an unbalanced mineral metabolism.

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P586

How well are guidelines followed in the follow-up of hypoparathyroid patients?

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Background

Hypoparathyroidism (HypoPT) is a rare condition that is characterized by hypocalcemia and hyperphosphatemia due to low or inappropriately normal serum levels of parathyroid hormone (PTH) for at least 6 months. The long-term complications of hypoparathyroidism indicate the necessity of screening them. In the follow-up of these patients according to hypoparathyroidism guidelines is recommended; calcium, phosphorus, albumin, magnesium, creatinine, and eGFR levels should be checked annually or more frequently than clinical status. A 24-hour urine calcium excretion is recommended once a year. Renal imaging is recommended in patients with elevated creatinine or high urinary calcium excretion, or patients suggesting renal stones. For basal ganglia calcification, brain MRI or CT is advised. A yearly eye examination is recommended for cataracts. In our study, in the long-term follow-up of hypoparathyroidism patients, it was examined whether the guidelines were followed.

Methods

Between February 2019 and September 2021, patients aged ≥ 18 years with hypoparathyroidism who were followed by the routine scheduled monitoring visit at the outpatient clinic of the endocrine and had their data retrospectively documented. Comorbidities, imaging, and hormonal tests and results of these patients were evaluated.

Results

Among the 264 patients, the mean age was 49.34 ± 12.98 (22-91). 211 (79.9%) of the participants were female. All patients' had blood biochemistry tests. Of the patients, 3% had eye examinations, 9.8% had brain imaging, 18.6% had renal imaging, 11 % had 24 h urinary Ca results. Cataract was observed in 2 (0.8%), basal ganglia calcification was observed in 4 patients (1.5%). Nephrocalcinosis or nephrolithiasis was observed in 2 patients (0.8%). Hypercalciuria was defined as a 24 h urine calcium excretion >300 mg/24 h and was observed in 8 of participants with hypoparathyroidism. (Table 1)

Table 1 Hypoparathyroidism complications screening

	Total ($n=264$)
Eye screening	8 (3)
Normal	5 (1.9)
Cataract	2 (0.8)
Glaucoma	1 (0.3)
Brain imaging	26 (9.8)
Normal	22 (8.3)
Calcification	4 (1.5)
Renal imaging	49 (18.6)
Normal	47 (17.8)
Renal stone	2 (0.8)
24 h Urinary Ca	29 (11)
24 h Urine Ca normal (<300 mg/24 h)	21
24 h Urine Ca elevated(>300 mg/24 h)	8

Conclusion

In the follow-up of patients with hypoparathyroidism, the guidelines cannot be followed much in intensive outpatient clinic conditions. These patients screening for complications is as important as blood tests.

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P587

Serum Vitamin D Levels in a Group of Migraine Patients Compared With Healthy Controls: A Case–Control Study

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Objective

Migraine is a common primary headache disorder that affects 12-15% of the general population. Also, vitamin D deficiency is a global health problem. A few studies have shown relationship between serum vitamin D levels and headache. The aim of this study was to investigate the difference in serum levels of 25-Hdroxy vitamin d [25(OH)D] between migraine patients and healthy controls and also to determine the relationship of vitamin D deficiency with frequency and severity of migraine.

Materials and Methods

204 newly diagnosed migraine patients and age- and sex- matched 204 control subjects were enrolled in this case -control study. Migraine diagnosis was settled according to the International Classification of Headache Disorders-III diagnostic criteria. The demographic and clinical data (migraine subtypes, frequency and severity of migraine) of the participants were recorded. Blood samples were obtained and 25(OH)D serum concentrations were determined using enzyme-linked immunosorbent assay (ELISA). Serum 25(OH)D $\leq$ 20, 21-29 and ≥ 30 ng/ml were considered deficient, insufficient, and sufficient, respectively.

Results

The mean concentration of 25(OH)D was 15.30 ± 9.93 ng/ml in migraine group and 14.62 ± 7.93 in controls. There was no significant difference in 25(OH)D concentration between migraine group and controls ($P=0.443$). There was no correlation between 25(OH)D level and headache characteristics including aura, attack severity and frequency ($P>0.05$). The number of subjects with vitamin d deficiency and insufficiency was similar between migraine group and controls ($P=0.365$).

Conclusions

We did not find significant difference in vitamin D levels among between case and controls. Also no significant correlation was noted between headache parameters (frequency and severity) and serum vitamin D levels. Further studies with larger sample sizes are required to confirm our results.

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P588

Vitamin D deficiency persists despite rising use of vitamin D supplements in Western Greece

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Introduction

Use of supplements (VDS) and vitamin-D measurements have been rising in the recent past globally. Despite increasing intake, our observations reveal that a

large percentage of the population remains deficient (VDD). We designed the present real-world study, to address this controversy.
Methods
We collected data from patients attending our clinics between March 2014 and December 2022. We recorded our subjects' gender, age, history of VDS use, duration and dose, and vitamin-D measurements, when available. We estimated the ratio of patients with vitamin-D adequacy (>30ng/ml) (VDA) by year and month of measurement, stratified by the dose of VDS intake: low-dose ($\leq$ 1200IU/day)(LD), medium-dose (1201-3000IU/day)(MD), high-dose (>3000IU/day)(HD), duration of intake: short-term-use($<$12months), long-term-use ($\geq$12months)(LT), and use at present: current-users(CU), past-users(discontinued for $\geq$2months)(FU), non-users(NU).
Results
Out of 10,292patients, data on VDS intake were available in $n=8605$ patients(83.6%): NU, $n=7212$(71.4%), FU, $n=566$(5.6%) and CU, $n=827$ (8.2%). Vitamin-D measurements were available in $n=6912$ patients (67.2%); NU $n=5644$ (81.7%), FU $n=507$ (7.3%), CU $n=761$ (11.0%). Vitamin-D measurement was available in 42.1% of patients in 2014 rising gradually to 86.8% in 2022, $P<0.001$. The cohort's mean vitamin-D was 23.1 ± 9.1ng/ml. VDD was found in $n=5401$ (78.1%). VDD was identified in 55.2% of CU, 76.8% of FU and 84.5% of NU ($P<0.001$). The rate of VDD went down with the dose of VDS used both in FU(LD 83.9%, MD 78.8%, HD 73.0%, $P<0.05$) and CU (LD 60.1%, MD 53.2%, HD 51.9%, $P<0.05$). The rate of VDD reached its nadir in August(62.1%) and September(61.2%), but rose to >70% in October and >80% during the remaining months, $P<0.001$. Intake of VDS at any time went up from 2.9% in 2014 to 35.2% in 2022($P<0.001$), and the VDD rate went down from 85.2% in 2014, to 74.5% in 2022. The serum vitamin-D increased from 21.7 ± 9.0ng/ml in 2014 to 25.0 ± 10.3ng/ml in 2022, $P<0.001$. Longer duration of VDS intake lowered the risk of VDD (LT vs ST use OR 0.51, 95%CI 0.38-0.69, $P<0.0001$). LT use of VDS in HD yielded the lowest risk (30.2%), while ST and LT use of VDS in LD yielded the highest risk of VDD (81.6% and 83.3% respectively).
Conclusions
Despite a gradual increase in vitamin-D measurements, and VDS intake, most patients attending our clinics remain VDD. A modestly effective strategy in controlling that epidemic is the long-term intake of higher doses of VDS, but efficacy goes down shortly after stopping treatment. Studies are urgently in need to solve this major global health issue.

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P589

Denosumab for Osteoporosis in Patients With Primary Hyperparathyroidism in a Tertiary Hospital in Spain

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Introduction
Osteoporosis is a frequent complication associated with primary hyperparathyroidism (PHPT), and surgery is the most effective treatment once established. However, many patients are not candidates for it, and different medical options have been investigated. We aimed to assess the efficacy of denosumab (DMAB) in increasing bone mineral density (BMD) and preventing PHPT-related complications.
Methods
Case-control study defining cases (Group 1 G1) as those patients who received DMAB and control (Group 2 G2) as those who had undergone surgery or had received bisphosphonate treatment.
Results
17 patients of G1 with a mean age of 75,71 years and 56 patients of G2 with a mean age of 62,90 years ($P<0,0001$) were recruited. The mean follow-up time for G1 was 2 years and for G2 was 3,2 years. At baseline total serum calcium and normalized ionic serum calcium mean were 9,77 mg/dl and 1,34 mmol/l in G1 vs 10,32 mg/dl and 1,44 mmol/l in G2 ($P=0,001$). PTH mean level was 80,88 pg/ml in G1 and 108,89 in G2 ($P=0,008$). 8 (47.06%) patients from G1 vs 11 (19.64%) patients from G2 had undergone parathyroidectomy before follow-up ($P=0,024$), and 2 (11.76%) patients from G1 vs 25 (44.64%) patients from G2 underwent surgery during follow-up ($P=0,01$). At the follow-up end levels of total calcium and ionized calcium decreased -1,52% and -1,81% in G1 vs -8,44% and -14,54% in G2. PTH levels increased 61,64% in G1 and decreased 28,04% in G2. Patients showed an increase in BMD at the lumbar spine by 6.51% in G1 and 4.63% in G2. In the distal third of the radius, BMD decreased by 0.29% in G1 and 0.25% in G2 ($P=0,986$). Only in G2 did BMD increase by 4.04% in the femoral neck and 2.42% for the total neck. No skeletal fractures or treatment-related adverse events were observed during the follow-up. Only 26.79% of patients in G2 had nephrolithiasis after follow-up.
Conclusions
Denosumab treatment is safe and effective in preserving BMD, especially in the lumbar spine in those patients with PHPT who have a contraindication to undergo parathyroidectomy.

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P590

Post-thyroidectomy development of posterior reversible encephalopathy syndrome (PRES) due to over-replacement of hypocalcemia

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A 61-year-old woman was admitted to the Emergency Department with generalized seizures. She reported general malaise, anorexia, headache and multiple episodes of vomiting that started about 12 h before admission. She had a history of recent thyroidectomy, and she was on oral calcium carbonate (3 gr/day) and alpha calcidol (3 mg/day). Non-contrast head CT scan was negative for major findings. Laboratory work up revealed hypercalcemia (corrected calcium 14,4 mg/dl), renal impairment (creatinine 2.9 mg/dl) and compensated metabolic alkalosis. Further neurological workup with brain MRI revealed cortical swelling and FLAIR signal abnormalities of both occipital, parietal and right frontal lobes, consistent with posterior reversible encephalopathy syndrome (PRES). The patient's encephalopathy resolved after resolution of hypercalcemia and she had no neurological deficits on discharge. She was restarted on lower doses of calcium for hypoparathyroidism and is on close follow-up. This case illustrates the difficulties in managing postoperative hypoparathyroidism and highlights a rare but serious complication of iatrogenic hypercalcemia.

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P591

Abstract withdrawn

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Clinical Features of Patients with Primary Hyperparathyroidism in Mugla: A Single-Center Experience

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Introduction
Primary hyperparathyroidism (pHPT) is the third most frequently seen endocrine disease with autonomous overproduction of parathyroid hormone (PTH) in one or

more parathyroid glands. It's associated with osteoporosis, bone fractures, nephrolithiasis, renal failure and increased cardiovascular risk. We aimed to investigate the distribution of the clinical manifestations and biochemical features in patients with pHPT.
Methods
A retrospective study was performed in 156 patients [19M (12.2%)/137F (87.8%)] with pHPT. The patients' comorbidities, complications, laboratory results, preoperative imaging findings and postoperative pathology results were recorded.
Results
The mean age of the patients was 59.49 ± 12.38 years. The mean calcium level was 11.12 ± 1.05 mg/dl, the mean phosphorus level was 2.63 ± 0.54 mg/dl, the mean parathormone level was 176.12 ± 237.34 pg/ml, the mean 25(OH)D level was 22.19 ± 11.49 ng/ml. Among patients, 70 (45%) had hypertension, 81 (51.9%) had osteoporosis, 46 (29.9%) had nephrolithiasis, 20 (12.9%) had a history of bone fracture. 19 of the patients (12.1%) had normocalcemic primary hyperparathyroidism with normal serum calcium and elevated PTH levels (NHPT). Of the patients with NHPT, 14 (73.7%) had hypertension, 11 (57.9%) patients had osteoporosis, 3 (15.8%) had nephrolithiasis and 4 (21.0%) had a history of bone fracture. The location of abnormal parathyroid gland was found in the ultrasound of 85 patients (62.5%) and in the parathyroid scintigraphy of 81 patients (63.3%). 73 patients (46.7%) were operated and among them, 68 patients had adenoma and 5 had hyperplasia in pathology reports. Among patients undergone surgery, 7 parathyroid adenomas were located in the right superior, 26 in the right inferior, 6 in left superior, 27 in left inferior part of the thyroid gland.
Discussion
The profile of pHPT is changing with older age at presentation. The most common complications of pHPT patients were osteoporosis and nephrolithiasis consistent with the literature. The emergence of nephrolithiasis and bone fracture is decreasing. The prevalence of NHPT was higher than other studies reporting prevalance between 0.5% and 0.7%. Complications such as osteoporosis and bone fracture were also commonly observed in patients with NHPT.
Conclusion
Most patients with PHPT in Mugla still exhibit classic clinical and biochemical features. Due to increased risk of complications in NPHPT patients, their complications should be well screened.

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Densitometry misinterpretation leading to unnecessary denosumab prescription

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Background
Bone mineral density (BMD) measurement is an important tool for fracture risk assessment, but should be used with awareness of its performance and analysis pitfalls.
Case Presentation
A 59-year-old patient underwent her first densitometry as part of a routine medical check-up. She had no previous fractures and no risk factors that could impair bone health. The results showed that her BMD was in the range of low bone mass. Four years later, densitometry was performed again with the same device, but without calibration for the least significant change. Based on the very low T-score of -3.7 at the lumbar spine, osteoporosis was diagnosed and denosumab therapy was initiated. There were no newly acquired comorbidities, and secondary causes of osteoporosis were not investigated. The third densitometry was performed a year later, at the age of 64, before she came to our clinic. This time, a lumbar spine T-score of -2.3 was obtained with a different device. This was again discordant to the second densitometry, as such a rapid improvement after the administered therapy would not be expected. We reviewed all three densitometry reports and found that her second densitometry, which showed osteoporosis, had incorrect vertebral labelling: Th12-L3 were measured instead of L1-L4. Even without taking into account that she had previously received three denosumab doses, the Fracture Risk Assessment Tool was low and estimated 5.1% risk of major osteoporotic and 0.5% risk of hip fractures. It was evident that she did not need osteoporosis treatment. Although the risk of rebound effects after short-term denosumab therapy and low C-telopeptide was low, we gave her a dose of zoledronate seven months after the last denosumab application.
Conclusions
Justified indications for BMD (re)testing, careful analysis of results and interpretation of reports are mandatory to avoid overdiagnosis and misdiagnosis of osteoporosis, which could lead to ineffective, costly, and even damaging consequences.

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The clinical and etiological aspects of primary hyperparathyroidism

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Introduction
Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by inappropriate secretion of parathyroid hormone leading to hypercalcemia. The aim of our study is to evaluate the clinical and etiological aspects of PHPT in our series.
Methods
This is a retrospective descriptive study including 32 patients followed for PHPT at the endocrinology department of the military hospital of Tunisia between January 2018 and December 2022. Clinical and paraclinical data were collected from medical records.
Results
The mean age was 59,4 ± 13 years with a predominance of women: sex ratio (H/F) = 0,68. PHPT was discovered fortuitously by a routinely biological check-up in 40,6% of cases and by an incidentaloma in 15,6% of cases. The diagnosis of PHPT was revealed by complications in 28,1% of cases (bone pain in 25% of cases, renal lithiasis in 3,1% of cases) and by the presence of general signs related to hypercalcaemia in 15,6% of cases. The mean calcemia was 2.98 ± 0,36 mmol/l with severe hypercalcemia (up to 3.5 mmol/l) in 9.4 % cases. Patients had hypophosphoremia in 19,4 % of cases and hypercalciuria in 60,8% of cases. The mean parathormone level was 292,9 ± 322,2pg/ml. The mean 25-OH-vitamin D level was 16.23 ± 9,05ug/dl. Normocalcemic HPTP was present in one case. Renal ultrasound showed lithiasis in 53% of cases. None of the patients had nephrocalcinosis. Thirty-four percent of cases had renal insufficiency. Bone densitometry revealed osteoporosis in 9.4% of cases, osteopenia in 50% of cases and was normal in 40.6% of cases. A cervical ultrasonography associated with a Technicium-SestaMIBI parathyroid scintigraphy was performed in all our patients. The etiologies identified were a parathyroid adenoma in 75% of cases and parathyroid hyperplasia in 25% of cases among which one case of multiple endocrine neoplasia type 1.
Conclusion
Most often, the presentation of PHPT is asymptomatic with the advent of the routine measurement of serum calcium. A rigorous etiological assessment and screening for complications is needed to provide optimal management.

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Therapeutic and evolutive aspects of primary hyperparathyroidism

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Introduction
Surgery is the only curative treatment for primary hyperparathyroidism (PHPT). However, some patients may present a persistence or a recurrence after surgical treatment. The aim of our study was to evaluate the therapeutic and evolutive aspects of PHPT after the first surgery.
Methods
A retrospective study was conducted at the endocrinology department of military hospital of Tunis including 32 patients diagnosed with PHPT over a period of four years (between 2018 and 2022). Clinical and paraclinical data were collected from medical records.
Results
Our population was composed of 13 men and 19 women with a mean age of 59 ± 13 years old. The mean parathormone (PTH) level was 292 ± 322 pg/ml. The mean calcemia was 3 ± 0,4 mmol/l. All our patients received rehydration. Three percent were treated with bisphosphonates. Nineteen patients underwent surgery. Adenectomy was performed for 17 patients and removal of 3/4 of the parathyroids for two patients. The anatomopathological examination revealed parathyroid

adenoma in 75% of cases and parathyroid hyperplasia in 25% of patients. Regarding patients who have underwent surgery, the evolution was marked by a remission rate in 42% of cases. Persistence of PHPT was observed in 10 patients (53%). Among these patients, three had multiple adenomas, one had an ectopic adenoma of the superior mediastinum and six had hyperplasia of other parathyroids. Recurrence of PHPT was observed in one patient who had hyperplasia of parathyroids related to multiple endocrine neoplasia type 1.
Conclusion
Persistence and recurrence rates highlight the importance of preoperative topographic investigation and intraoperative PTH measurement to improve the prognosis of PHPT.

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Surgery of primary hyperparathyroidism during pregnancy: case series

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Background
Primary hyperparathyroidism can occur at any age, the typical patient is a postmenopausal woman, primary hyperparathyroidsim is found rare by pregnant women. The maternal symptoms are similar to the symptoms by postmenopausal women.
Materials and methods
Among the years 2000-2022 we have performed 3459 operations (including 6,6% reoperations) with diagnosis of hyperparathyroidism, there were six women, who underwent parathyroidectomy during pregnancy. The median maternal age was 30 years. All women had before operation localization of adenoma by ultrasonography, one woman had localization by the MRI. All woman were operated during the second trimester. Postoperative care was without complication, two patients had parestezie. All patient had genetic testing before or after the operation.
Result
Incidence of primary hyperparathyroidism by pregnant women is rare. By the diagnosis of primary hyperparathyroidism is indicated surgical therapy. The base of localization examination by pregnant women is examination of ultrasonography. Operation in pregnancy would be due in the second trimester. By pregnant women always due the genetic tests.

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Better late than never - a very rare cause of short stature

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Introduction
X-linked hypophosphatemic rickets (XLH) is a very rare cause of growth deficiency that can be diagnosed even in adulthood. The mutation of the PHEX gene in these patients causes higher levels of FGF-23 and hypophosphatemia.
Case presentation
A 20-year-old male patient was admitted into our clinic due to short stature, walking difficulties, joint and muscle pain, predominantly in the lower limbs. He described the presence of symptoms since childhood. The family history revealed that his mother, aunt and maternal grandfather had short stature with similar appearance. In paediatrics service he was diagnosed with familial hypophosphatemic rickets at the age of two and was treated with 1-alpha(OH)D3 and a rich phosphorus diet until the age of seven. No genetic or FGF- 23 testing was performed at that time. On physical exam, the patient had a height of 156 cm, a disharmonic dwarfism, many dental abscesses, waddling gait, genu varum and lower limbs deformities. The laboratory tests showed a normal serum calcium and hypophosphatemia with FePO4 of 24%. Radiological findings revealed bilateral coxarthrosis and genu varum. Due to heredity, XLH was the most likely diagnosis in this case. FGF-23 was in the upper normal range confirming the diagnosis. Genetic testing and counselling were recommended, for the analysis of the PHEX gene mutation, due to the desire of this patient to have a child.
Conclusion
Being so rare, XHL as a cause of short stature can be easily overlooked. XLH should be considered in the differential diagnosis of short stature with low serum phosphate, regardless of age.

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Diabetes, Obesity, Metabolism and Nutrition

P53

The concentration of Polycyclic Aromatic Hydrocarbons (PAHs) in human serum and adipose tissues and In Vitro stimulatory effect of naphthalene in adipogenesis in 3T3-L1 cells

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Polycyclic aromatic hydrocarbons (PAHs) are common environmental pollutants derived from the incomplete combustion of organic materials. In urban and industrial areas, level of pollution with these compounds is high, which leads to numerous negative health effects. Some literature data indicate the involvement of PAHs in the development of obesity, however, there is no data showing the distribution patterns of PAHs in human adipose tissue (AT) and their impact on the process of adipogenesis. The aim of our study was to investigate the concentration of 16 priority PAHs in the plasma and three types of AT: mesenteric, omental, and subcutaneous in French and Polish bariatric patients ($n = 10$ per group). Next, we analyzed correlation between concentration of the four most abundant PAHs and BMI of patients as well level of adipokines in plasma and AT. Using the mouse preadipocytes 3T3-L1 cell line we determined the dose-dependent effect of naphthalene (1-500 ng/ml) on adipocytes viability (CK-8 assay), proliferation (BrdU assay) and differentiation (Red oil staining, qRT-PCR) as well effect on its endocrine function (ELISA assay) ($n = 6$). Statistical analysis was carried out using the Student's t-test or one-way ANOVA to compare differences between group ($P \leq 0.05$) while correlations were analyzed with the Pearson correlation coefficient, two-tailed ($P \leq 0.05$). We observed that the concentrations of the 16 tested PAHs were higher in adipose tissue than in plasma, indicating bioaccumulation. In addition, in French patients, the concentration of naphthalene in both plasma and omental AT correlated with BMI as well as the concentration and expression of the gene for adiponectin, chemerin and resistin. We demonstrated for the first time that naphthalene stimulates viability and proliferation of 3T3-L1 cells. Moreover, it has a significant impact on the differentiation of preadipocytes by increasing lipid content in cells, upregulation of genes involved in adipogenesis, and stimulating chemerin secretion by differentiated 3T3-L1 cells. Taken together those findings, we conclude that PAHs and more particularly naphthalene could be an obesogen molecule and increase the risk of obesity. Funding: Study was supported by Région Centre Val de Loire (HAPOFERTI project number 32000496). Ewa Mlyczynska obtained funding as a part of PhD scholarship program—BGF doctorate from Campus France and Jagiellonian University programs: Excellence Initiative –Jagiellonian University.

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Continuous Glucose Monitoring in Hospitalized Type 2 Diabetes Patients

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Introduction
Continuous glucose monitoring systems (CGM) have revolutionized the monitoring of diabetes, allowing real-time measurement of interstitial glucose levels. Although these devices are suitable for patients on insulin therapy, they are not yet routinely used in an inpatient setting. The difficulty observed in the glycemic control of hospitalized patients under intensive insulin therapy led to the development of a protocol to study the application of CGM in these patients.
Aim
Primary endpoint was the increase in the time in range (glycemic readings between 100-180mg/dl) in hospitalized patients with CGM. Secondary endpoint was the reduction in the number of hypoglycemic events.
Methods
Prospective study of 60 hospitalized patients with type 2 diabetes on intensive insulin therapy. Patients were randomized into two groups of 30 individuals: an intervention group monitored through CGM (Freestyle Libre™ 2) and a control group whose glycemic profile was monitored using point-of-care capillary blood glucose (CBG), with at least three readings per day.
Results
Both groups were similar regarding age (74.4 years vs. 76.8 years, $P=0.277$), gender (higher prevalence of males, 83.3% vs. 63.3%, $P=0.143$), diabetes duration (12 years vs. 14 years, $P=0.824$), diabetes associated complications (assessed using the Diabetes Complications Severity Score; $P=0.151$) and outpatient treatment ($P=0.570$). No differences were observed on admission diagnosis (most frequently due to an infectious disease, 53.3% vs. 48.3%, $P=0.157$), nor regarding the analytical values on admission (namely hemoglobin: 12.6 mg/dl vs. 11, 7 mg/dl, $P=0.158$, HbA1c: 7.1% vs. 7.2%, $P=0.158$ and creatinine: 1.4 vs. 1.3, $P=0.158$). CGM had a positive impact on glycemic control, with more readings per day (6 vs. 4, $P<0.001$), improved time in range (100-180 mg/dl) (53.5% vs. 36.5%, $P=0.032$), and less time above range (26% vs. 53%, $P=0.008$), in particular values above 250 mg/dl (6% vs. 25%, $P=0.003$). A lower mean glucose (162 mg/dl vs. 207 mg/dl, $P<0.001$) and lower estimated HbA1c (7.3% vs. 8.8% $P=0.001$) were also observed in the CGM group, but there was no difference in glycemic variability (34.2% vs. 34.8% $P=0.181$). Regarding hypoglycemia, the small number of hypoglycemic events per patient in each group did not allow an adequate comparison (CGM 0 (0-5) vs. CBG 0 (0-2); $P=0.107$). CGM showed no difference in reducing mortality, length of hospital stays, nor infection rate, compared to CBG ($P=1.000$, $P=0.455$ and $P=0.606$, respectively).
Conclusion
The results obtained in this prospective study encourage the use of CGM in optimizing the control of type 2 diabetes during hospitalization.

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Ceramides In Epicardial Adipose Tissue from Coronary Diabetic Patients: New Markers of Tissue Metabolism?

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Ceramides (Cer), which are known to be altered in plasma before the onset of coronary artery disease (CAD), have been proposed as new markers for cardiovascular disease (CVD) risk. Serum Cer18:1/C16:0, Cer18:1/C18:0 and Cer18:1/C24:1 to Cer18:1/24:0 indexes are proposed to be indicative of CAD. Epicardial adipose tissue (EAT) is a visceral adipose tissue, surrounding and in direct contact with the myocardium and coronary arteries, which volume is considered a risk factor for CVD. Studies from our laboratory demonstrated an increase in EAT Cer total content from CAD patients. We also reported an increase in Lipoprotein Lipase (LPL) activity in EAT from CAD and Diabetes Mellitus 2 (DM2) patients, suggesting that LPL would be involved in EAT expansion. EAT Cer content was directly associated with LPL activity. Our aim was to evaluate the association between EAT Cer indexes and LPL activity, and markers of EAT lipid metabolism, in CAD patients with and without DM2.
Methods
Patients undergoing coronary by-pass graft (CAD, $n=24$), with and without DM2 (DM2, $n=7$; No-DM2, $n=17$), and patients without CAD (noCAD, $n=13$) were studied. In EAT, LPL activity, Angiopoietin-like protein 4, Glycosylphosphatidylinositol anchored high density lipoprotein binding protein-1 (GPIHBP1), Peroxisome Proliferator Activated Receptor γ (PPARγ), VLDL-Receptor(R) and Fatty Acid Binding Protein-4 expression were assessed. Tissue lipidome was evaluated by UHPLC-MS.
Results
CAD-DM2 patients presented a deleterious and atherogenic metabolic profile compared to the other groups. CAD-No DM2 and CAD-DM2 presented a higher Cer18:1/C24:1 to Cer18:1/24:0 index than noCAD ($P=0.017$ and $P=0.003$ respectively), with no differences between CAD diabetic and CAD no diabetic patients. This index was directly associated with LPL activity ($r=0.373$, $P=0.042$), PPARγ ($r=0.637$, $P=0.009$), GPIHBP1 ($r=0.497$, $P=0.18$) and VLDL-R ($r=0.441$, $P=0.031$). No differences were found among groups neither in Cer18:1/C16:0 nor Cer18:1/C18:0 to Cer18:1/24:0 indexes.
Conclusion
This is the first time that a relation between LPL, its regulators and Cer is reported in AT. EAT Cer indexes could be suggested as markers of the tissue metabolism in CAD and DM2.

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Long-Term Diabetes Remission Rates In A Group of Type 2 Diabetic Patients After Sleeve Gastrectomy and Rou and Y Bypass Metabolic Surgery: A Single-Centered Experience

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Introduction
Various rates were reported regarding diabetes remission and improvement in hyperglycemia in many studies from different populations. Determinants of diabetes remission have not been definitively established so far. In this study, we aimed to evaluate the long-term glycemic status after bariatric surgery in diabetic obese patients followed by Marmara University Endocrinology Outpatient Clinic.
Method
The retrospective study included 233 type 2 diabetic obese patients who underwent either sleeve gastrectomy or gastric bypass between 2011-2021. Preoperative, postoperative sixth month, first year, and second year data were collected from the patient files. In the analysis of the dependent variables, patients who fulfilled whole visits were included. The glycemic status of diabetic patients at postoperative first and second year visits was classified as complete remission, partial remission, recovery, no change, and recurrence in accordance with the criteria of the American Society of Bariatric and Metabolic Surgery, 2022. Remission ratios were calculated for each visit, seperately. Logistic regression was used to analyse the factors affecting diabetes remission for the whole diabetic group.
Results
Postoperative BMI values were significantly lower than the preoperative level ($P<0,001$), additionally remained similar between the first and the second years. BMI change was found to be similar between gastric bypass and sleeve gastrectomy. Fasting blood glucose and HbA1c levels were significantly lower than the preoperative levels as well ($P<0,001$). 24.9% ($n=58$) of the patients were on insulin preoperatively. This ratio was found to be 3.5% ($n=6$) in the first year and 3.3% ($n=4$) in the second year. Complete remission rate was 68.0% ($n=132$) in the first year. In the second year, complete remission and recurrence rates were 59.5% ($n=72$) and 8.3% ($n=10$), respectively. Remission rates were similar among the two surgical procedures. To determine the factors affecting remission across the whole sample, a regression model was conducted. Duration of diabetes, preoperative insulin usage, preoperative BMI, and the type of the surgery were included in the model. Preoperative insulin use of patients was associated to diabetes remission outcomes. Patients who were not taking insulin before the surgery were more likely to experience postoperative diabetes remission (OR=7.523, $P<0.001$, 95%CI 3,075-18.404 for the 1st year; OR=5.096, $P=0.002$, 95%CI 1.781-14.577 for the 2nd year).

Conclusion
At the postoperative first and second year checkpoints, complete remisson rates were 68.0% and 59.5%, and recurrence rate was 8.3% in the second year. Not using insulin preoperatively made the probability of diabetes remission 5.1 times higher.

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A Quality Improvement initiative to assess differences of diabetic ketoacidosis (DKA) management across hospitals in the United Kingdom

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Background
Joint British Diabetes Societies (JBDS) have developed guidelines for the treatment and management of diabetic ketoacidosis (DKA) in adults in the United Kingdom (UK). Multiple single center audits are known to assess compliance to guidelines. However, unified data on DKA management across multiple centers is unknown.
Aims
To study the precipitating factors and assess for differences in DKA management across UK hospitals.
Methods
A retrospective analysis of 443 DKA admissions across six hospitals between October 2021 and September 2022 was undertaken. DKA was defined as all of: glucose >11 mmol/l or known diabetes, bicarbonate <15 mmol/l and/or venous pH <7.3, blood ketones >3 mmol/l and/or urinary ketones $++$ or more. Patients <16 years or who self-discharged before the DKA resolution were excluded. Data on precipitating factors, fixed rate intravenous insulin infusion (FRIII), fluids prescription, hourly glucose and ketone monitoring were collected. Differences in management across hospitals was analyzed using Kruskal-Wallis Test. Deviations from guidelines are expressed in percentage. 100% represents optimal adherence whilst values below and above 100% indicate that measures applied were less than or more than recommended respectively. A p value of <0.05 was considered significant.
Results
Since the objective is to identify best practice and not to compare, hospitals are coded A to F to ensure anonymity. Variations were found in fluid prescription (A – 92.1%, B – 101.3%, C - 89.7%, D – 76.0%, E – 98.3%, F – 115.5%; $P=<0.001$), glucose monitoring(A – 103.1%, B -86.1, C- 88.9%, D - 106.4%, E – 99.2%, F – 95.7%; $P=<0.001$) and ketones monitoring(A – 71.5%, B – 85.1%, C – 70.0%, D – 59.3%, E - 65.0%, F- 85.7%; $P=<0.001$). No significant difference was found between hospitals in FRIII prescription (A- 99.5%, B – 100.0%, C – 100.0%, D – 100.0%, E – 93.9%, F-99.8%; $P=$ 0.064). Intercurrent illness(36.6%), suboptimal compliance(32.1%), COVID(3.6%), drugs (0.2%), immunotherapy (0.2%), first presentation of diabetes (8.8%), sepsis (2.9%), SGLT2 (0.9%), surgery (0.9%), undetermined (12.0%) were the precipitating aetiologies recorded.
Conclusion
Suboptimal concordance with recommended treatment and intercurrent illness were the common precipitating factors for DKA across sites. Despite common guidelines and similar precipitating factors, significant inter-hospital variation in DKA management was observed across hospitals. Establishment of a centralized registry coupled with regular stakeholder feedback could help minimize interhospital variation and improve patient outcomes.

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Vitamin B12 and diabetic peripheral neuropathy in type 2 diabetic patients

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Introduction
Metformin is a cornerstone in the treatment of type 2 diabetes, but in recent years several studies have shown that metformin use is associated with a 4-24% decrease in vitamin B12 levels. It is estimated that this problem occurs in approximately 10-30% of patients using metformin and may contribute to distal symmetrical polyneuropathy (DSPN), a very common and clinically relevant diabetic complication.
Objective
To study vitamin B12 concentrations in type 2 diabetic patients receiving metformin and presenting with DSPN.
Patients and methods
A cross-sectional study was conducted over a period of 19 months, from 1 February 2021 to 30 September 2022, including 123 type 2 diabetic patients treated with metformin consulting at the National Institute Zouhaier Kallel Tunisia. The presence of DSPN was determined by the "douleur neuropathique" DN4 test and its severity was assessed by the Toronto Clinical Neuropathy Score(TCSS). Vitamin B12 and folate levels were determinated for all participants.
Results
The mean age of our population was 60.99 $\pm$ 6.85 years (81 females and 42 males). The mean average DN 4 score and TCSS score were 5.31 $\pm$ 1.21 and 9.5 $\pm$ 3.36, respectively. The mean duration of metformin use was 14.6 ± 7.27 years with a mean dose of 1923 ± 575.4 mg/day. Fifty seven percent of patients had mild neuropathy, 23.5% moderate neuropathy and 19.5% severe neuropathy. The mean serum Vitamin B12 level was 353.77 $\pm$ 178.22 pg/ml with extremes ranging from 64.47 to 918.4 pg/ml. Eighteen and a half percent of the population had a vitamin B12 deficiency (level <200 pg/ml) and 29.8% had a borderline level (level between 200 and 300 pg/ml). The Mean average of vitamin B12 level was 387,73 $\pm$ 190.97 in mild neuropathy, 319,04 $\pm$ 151,54 in moderate neuropathy and et 296,72 $\pm$178,22 in severe neuropathy. There was correlation between TCSS and vitamin B12 levels ($P=0.016$). Daily metformin dose and duration did not correlate with TCSS ($P=0.8$ and 0.45 respectively) or vitamin B12 levels.
Conclusion
Our study shows a positive association between vitamin B12 deficiency and the severity of neuropathy in type 2 diabetic patients on metformin. Therefore, We recommand a regular screening for vitamin B12 deficiency. Deficient patients were supplemented with parenteral vitamin B12. We consider a control of TCSS and DN 4 score 6 months later.

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Abstract withdrawn

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Diabetes and associated risk factors for cardiovascular mortality in Cuba: prospective study of 146,556 participants

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Background
Cardiovascular disease accounts for about one-third of all premature deaths (ie, age <70) in Cuba. Yet, the relevance of major risk factors, including diabetes,

systolic blood pressure (SBP), and body-mass index (BMI), to cardiovascular mortality in this population remains unclear.
Methods
In 1996–2002, 146,556 adults were recruited from the general population in five areas of Cuba. Participants were interviewed, measured (height, weight and blood pressure) and followed up by electronic linkage to national death registries until Jan 1, 2017; in 2006–08, 24,345 participants were resurveyed. After excluding all with missing data, cardiovascular disease at recruitment, and those who died in the first 5 years, Cox regression (adjusted for age, sex, education, smoking, alcohol and, where appropriate, BMI) was used to relate cardiovascular mortality rate ratios (RRs) at ages 35–79 years to SBP, diabetes and BMI; RR were corrected for regression dilution to give associations with long-term average (ie, "usual') levels of SBP and BMI.
Results
After exclusions, there were 125,939 participants (mean age 53 [SD12]; 55% women). Mean SBP was 124 mmHg (SD15), 5% had diabetes, and mean BMI was 24.2 kg/m^2 (SD3.6); mean SBP and diabetes prevalence at recruitment were both strongly related to BMI. During follow-up, there were 4112 cardiovascular deaths (2032 ischemic heart disease, 832 stroke, and 1248 other). Cardiovascular mortality was positively associated with SBP (>=120mmHg), diabetes, and BMI (>=22.5 kg/m2): 20 mmHg higher usual SBP about doubled cardiovascular mortality (RR 2.02, 95%CI 1.88–2.18]), as did diabetes (2.15, 1.95–2.37), and 10 kg/m2 higher usual BMI (1.92, 1.64–2.25). RR were similar in men and in women. The association with BMI and cardiovascular mortality was almost completely attenuated following adjustment for the mediating effect of SBP. Elevated SBP (>=120 mmHg), diabetes and raised BMI (>=22.5 kg/m2) accounted for 27%, 14%, and 16% of cardiovascular deaths, respectively.
Conclusions
This large prospective study provides direct evidence for the effects of these major risk factors on cardiovascular mortality in Cuba. Despite comparatively low levels of these risk factors by international standards, the strength of their association with cardiovascular death means they nevertheless exert a substantial impact on premature mortality in Cuba.
Keywords
Cuba, Cardiovascular, Diabetes, Body-mass index, Blood pressure.
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The dual GIP/GLP-1 receptor co-agonist Tirzepatide vs GLP-1 receptor agonists as add-on to basal insulin in uncontrolled type 2 diabetes mellitus: A rapid review of randomized controlled trials and meta-analysis

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Tirzepatide, a once-weekly dual co-agonist of Glucose-Dependent Insulinotropic Polypeptide (GIP) and Glucagon-Like Peptide 1 (GLP-1) receptors, has been demonstrated to improve glucose control and reduced body weight in different therapeutic approaches. With this rapid review and meta-analysis, we systematically reviewed the efficacy and safety of injectable incretin-based therapy added to basal insulin compared to basal insulin plus background treatments titrated rigorously to target fasting glycemia. The results were reviewed considering data from the SURPASS-5 trial, which demonstrated that Tirzepatide, in add-on to basal insulin, significantly improves several glycemic and extra glycemic endpoints. Eleven randomized clinical trials were identified and included in the meta-analysis. GLP-1 receptor agonists (GLP-1RAs) or Tirzepatide added to basal insulin than rigorously titrated basal insulin significantly ameliorates glucose control (Δ HbA1c = -1%, 95% CI -1.25; -0.74, I2 94%; Δ FPG = -14.6 mg/dl, 95% CI -21.6-; -7.6, I2 90%). Moreover, the chance to achieve optimal glucose control (i.e., HbA1c <7%) is significantly higher in the former treatment (RR 2.62, 95% CI 2.10; 3.26, I2 89%). GLP-1RAs or Tirzepatide added to basal insulin than rigorously titrated basal insulin significantly reduces body weight significantly (Δ weight = -3.95 kg, 95% CI -5.1, -2.79, I2 96%) without affecting the risk of hypoglycemia (Rr=1.01, 95% CI 0.86; 1.18, I2 7.7%). More precisely, Tirzepatide provides an impressive weight loss in a dose-dependent manner (-7.6 kg with Tirzepatide 5 mg/week, and -12.6 kg with 15 mg/week), exceeding the weight loss observed with GLP-1RAs. Injectable incretin-based therapy plus basal insulin remains a potent and safe therapeutic approach in uncontrolled type 2 diabetes previously treated with basal insulin. Thanks to a potent antihyperglycemic effect and an impressive induction of weight loss, Tirzepatide is expected to ameliorate the management of "diabesity" in these usually difficult-to-treat patients.
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Utility of using Continuous Glucose Monitoring based MetaSense in OneCare Diabetes care program in driving the metabolic outcomes in People with Diabetes Mellitus – A real world data from urban India

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Background
As adoption of continuous glucose monitoring (CGM) continues to expand, lot more studies are investigating the effects of CGM on HbA1C and hypoglycaemia risks in people with Diabetes Mellitus (PwD). In PwD, established benefits of usage of CGM along with digital diabetes self-management and education (DSME) program in Indian real-world context are scarce. OneCare compares patients engaged in its "IMPACT" DSME program alone vs program assisted by CGM.
Methods
A proof-of-concept, prospective study was conducted in PwD enrolled in the OneCare IMPACT program for 12 weeks. It is a virtual, personalized lifestyle program to support diabetes self-management through team of CDEs, yoga and physical trainer, emotional wellness coach and OneCare app to track patients' everyday physical activity, self-monitoring of blood glucose, and dietary patterns. Patients in the group 1 (n=30) received the regular IMPACT program, while those in group 2 (n=27) had CGM (Abbott Libre) inserted on enrolment in addition to the program. CGM data were used by the health coach to educate and engage patients, (MetaSense- a sophisticated software and service layer) in the program. Data on HbA1c, weight, CGM metrics, were used for analysis.
Results
Upon enrolment to IMPACT program, both the patient groups had a significant decline in HbA1c (%) [group1 from 8.3 to 7.3 (P= <.001); group2 from 9.4 to 6.9 (P= <.001)]. Among patients on CGM, only 25 % had TIR >70 %, 37% of patients had a Time below range <90mg/dl. MetaSense usage in group2, however led to significantly better mean reductions in HbA1c (%) vs group1 [2.51±2.17 Vs 0.91±1.05; (P= <.001) respectively]. A significant difference in mean weight reduction was observed in group assisted with and without MetaSense respectively [2.2±0.8 vs 0.81 ±1.86 (P<0.001)]. MetaSense usage significantly predicted reduction in HbA1c on a simple linear regression model [HbA1c reduction$n$=-.682+1.601*(MetaSense) where, MetaSense use: 0= No, 1 = Yes; (R^2 = .18, P= <.001)]. 18% of the variation in HbA1c is explained by MetaSense.
Conclusion
CGM can be a very useful tool to motivate, educate and teach PwD in clinical practice leading on to a better involvement of the patient in self-management issues. Addition of MetaSense to existing structed digital DSME "IMPACT' program leads to better outcomes with respect to HbA1c and weight. However many other factors may also be influencing the outcome of this study. Hence a well-planned study is encouraged to delineate the role of MetaSense.
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Left hemiparesis and urinary incontinence as presentation of pancreatic Insulinoma in a young female. A Case report and review of literature

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Introduction
Insulinoma is a rare tumor, with peak incidence at 30 -60 years of age and more frequent in women. It is associated with a myriad of clinical manifestations: from

clearly defined adrenergic and neuroglycopenic symptoms to asymptomatic hypoglycemia. We present the case of a 20-year-old patient with pancreatic insulinoma, which was surgically resected only after her second hospitalization due to repeated negative imaging.

Case presentation

A 20-year-old female patient presented in the Emergency Department in a stuporous state, following an episode of left hemiparesis, numbness and urinary incontinence. She had a three-month history of weakness and somnolence during the day but didn't suffer from any disease. Her blood glucose in admission was 24 mg/dl. After IV glucose administration, she recovered completely and was hospitalized for further evaluation of her hypoglycemia. During her hospital stay, she experienced episodes of tiredness and somnolence associated with fasting and postprandial hypoglycemia, in 2–3-hour intervals. In a blood sample after 8 h of fasting, her glucose was 24 mg/dl and insulin 17.4 µU/ml (≥ 3 µU/ml). Abdominal CT and MRI with contrast were negative. She was discharged from the hospital under diet tips for insulinoma to prevent hypoglycemia and Diazoxide treatment. Her low glycemic values continued despite the diet and up-titration of the Diazoxide dosage, which resulted in subsequent adverse reactions (palpebral edema, lip swelling, malaise and later, hirsutism). Having no improvement in her glycemic profile, Diazoxide was then stopped. In her second hospitalization 3 months later, her measured Insulin and C-peptide levels were very high with a blood glucose of merely 22 mg/dl. MRI with contrast identified a pancreatic lesion 11x9mm with no contrast enhancement. Surgical excision was performed and biopsy confirmed insulinoma. Glycemic values returned to the normal range but two weeks following surgery, our patient had acute pancreatitis and underwent a second surgical intervention. She discharged 2 weeks later in a good general condition.

Conclusion

Diagnosis of insulinoma in a young patient can be challenging, because the symptoms usually are atypical and nonspecific, and may precede the detection of a lesion. A careful imaging evaluation is necessary to identify the lesion early, with the aim of its surgical removal as soon as possible.

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P64

Covid-induced relapse of exogenous insulin autoimmune syndrome successfully treated with Rituximab and plasmapheresis

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Introduction

Exogenous insulin autoimmune syndrome (EIAS) is a rare cause of hypoglycemia in patients with diabetes treated with exogenous insulin. Flares of auto-immune diseases following covid-19 infection have been widely reported.

Case report

A 15-year-old type 1 diabetes female patient treated with detemir and glulisine was diagnosed with EIAS based on major glycemic instability and an elevated anti exogenous insulin autoantibody titer of 40 IU (NV < 0.4), after excluding other differentials. The evolution under high dose oral corticosteroids was favorable. Following a covid-19 infection there was a reappearance of severe nocturnal hypoglycemia and diurnal hyperglycemic phases concomitantly with an elevation of auto-antibody titer. The patient was treated with a course of rituximab 500mg twice followed by three sessions of plasma exchange. A clinical and biological remission was obtained (anti-insulin auto antibodies 4 IU/l).

Discussion

In recent years, the incidence of autoimmune hypoglycemia has gradually increased due to increased administration of exogenous insulin. Beside genetic susceptibility, immunogenicity is influenced by insulin type. There is still no consensus on EIAS management although most of authors recommend corticosteroids and immunosuppressants. Many studies hypothesized that SARS-cov2 may induce auto-immune responses. To our knowledge, this is the first report of EIAS relapse following covid-19 infection.

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P65

Gender differences in smoking cessation? Results of a randomized controlled trial of dulaglutide-assisted smoking cessation

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Introduction

Smoking harms women more than men and women seem to be less successful in quitting. Greater concerns about post-cessational weight in women and gender differences in craving and reward processing have been postulated as possible explanations. Our group recently showed that the GLP-1 analogue dulaglutide reduces post-cessational weight gain. We hypothesize that women compared to men might profit more from the weight-lowering effects of dulaglutide in terms of abstinence rates.

Methods

This is a predefined secondary analysis of a placebo-controlled, double-blind, single-center randomized trial including 255 daily smokers (155 women, 100 men). Participants received weekly dulaglutide (1.5mg) or placebo (0.9% sodium chloride) subcutaneous injections for 12 weeks in addition to standardized smoking cessation care. Smoking status was self-reported and confirmed by end-expiratory carbon monoxide measurement. We analyzed gender differences after 12 weeks of dulaglutide / placebo treatment in weight change, abstinence rates and craving assessed by a visual analogue scale (VAS, minimum 1, maximum 10). Additionally, fMRI was performed in a subset of participants and craving and neuronal activity in response to smoking cue videos were examined for gender differences.

Results

Median [IQR] age at inclusion was 42 [32,53] years in females and 44 [34,53] years in males. Mean (SD) BMI was 26.0 (5.0) kg/m^2 and 28.9 (4.9) kg/m^2, respectively. After 12 weeks, 61% of females in the dulaglutide and 65% in the placebo group were abstinent, compared to 66% and 64% of male participants. Among quitters, there were no gender differences in absolute or percentual weight change neither on dulaglutide (difference: 0.2 kg, 95%-CI [-1.2, 1.6]; $P = 0.762$ / 0.7%, 95%-CI [-0.9, 2.3]; $P = 0.382$) nor on placebo treatment (difference: 0.0 kg, 95%-CI [-1.0, 1.0]; $P = 0.954$ / -0.6 %, 95%-CI [-1.8, 0.6]; $P = 0.340$). There is no evidence for either a direct association of gender with change in craving (mean difference females vs. males: 0.05 points, 95%-CI [-1.34, 1.43], $P = 0.947$) or that the effect of gender on change in craving might depend on dulaglutide treatment (interaction term: $P = 0.712$). Smoking cessation was directly associated with a decline in craving (mean difference quitters vs. persistent smokers: -3.07 points, 95%-CI [-4.67, -1.47], $P < 0.001$); however, this did not depend on gender (interaction term: $P = 0.380$). Data of the fMRI substudy are currently being analyzed and will be presented at the congress.

Conclusion

Our data showed similar abstinence rates, post-cessational weight changes and craving intensity in females and males.

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P66

Weight Outcomes With Setmelanotide Over 3 Years in Patients With POMC or LEPR Deficiency Obesity

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Background

Rare variants in the melanocortin-4 receptor (MC4R) pathway are associated with early-onset, severe obesity and hyperphagia. Setmelanotide, an MC4R agonist,

reduced body mass index (BMI) and decreased hunger in patients with obesity due to biallelic variants in genes encoding proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) in Phase 3 trials. The current analysis assesses the durability of setmelanotide efficacy over 3 years in the subgroup of patients who achieved clinically beneficial weight loss.
Methods
Patients aged ≥6 years with POMC, including PCSK1, or LEPR deficiency obesity who demonstrated clinical benefit and acceptable safety after treatment with setmelanotide in a prior (index) trial continued treatment in a long-term extension trial (NCT03651765). Age-appropriate weight measures and safety were assessed. Changes in weight-related measures from index trial baseline were evaluated in patients who achieved ≥10% weight reduction (age ≥18 years) or ≥0.3-point BMI Z score reduction (age <18 years) after 1 year of treatment.
Results
Across all patients ($n=24$), mean (SD) percent changes in BMI were −24.8% (8.2%; $n=24$), −21.0% (13.0%; $n=23$), and −24.0% (17.9%; $n=15$) at 12, 24, and 36 months, respectively. In patients ≥18 years old ($n=11$), mean (SD) percent changes in weight were −25.1% (7.7%; $n=11$), −22.9% (12.5%; $n=11$), and −24.4% (13.2%; $n=8$) at 12, 24, and 36 months, respectively. In patients <18 years old ($n=13$), mean (SD) reductions in BMI Z score were observed at Month 12 (−1.31 [0.66]; $n=13$), 24 (−1.10 [0.79]; $n=11$), and 36 (−1.01 [1.22]; $n=4$). No new safety issues were observed during long-term treatment.
Conclusions
Patients who achieved ≥10% body weight or ≥0.3-point BMI Z score reduction at 1 year demonstrated persistent and clinically significant benefit at 3 years, supporting long-term use of setmelanotide in adult and pediatric patients with obesity due to POMC and LEPR deficiency.

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P67

Study of the prevalence, clinical correlates, and cardiovascular outcomes of central and primary hypogonadism in type 2 diabetes mellitus

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Background
In patients affected with type 2 diabetes mellitus (T2DM) a high prevalence of hypogonadism has been reported, even if there is no consensus on its metabolic and cardiovascular implications, especially according to the type of hypogonadism. The aim of this observational study is to evaluate: (1) the prevalence of different types of hypogonadism in T2DM according to validated criteria from the EMAS study; (2) look for correlations of gonadal status with severity or duration of diabetes, its complications, dyslipidemia, therapies, BMI, age and smoking habit; (3) the incidence according to the gonadal function of major adverse cardiovascular events (MACE) intended as acute coronary syndrome, cerebrovascular events and/or newly diagnosed coronaropathy requiring revascularization;
Patients and Methods
We evaluated 106 male patients, consecutively enrolled in diabetology clinics, between 18 and 80 years old; patients with already known pituitary or gonadal diseases, acute diseases, malnutrition, or using interfering drugs were excluded. Each patient underwent a complete evaluation of the gonadal axis including SHBG to define his gonadal status (according to EMAS criteria), a treadmill test, and information on diabetes and its complications, therapies, glucose and lipidic metabolism was collected. Only 7 began testosterone replacement therapy (TRT) after diagnosing hypogonadism. A follow up of 36 months was carried out to look for MACEs.
Results
We found evidence of hypogonadism in 49% of T2DM patients: 31% of them having hypogonadotropic forms (HH), and 18% having primary hypogonadism (PH). PH was found to be associated with higher age, and creatinine levels, whereas HH was directly correlated with BMI. Finally, we found a significant increase in MACEs at 36 months in HH compared to other patients (Fisher test $P=0.047$), no one after the beginning of testosterone treatment.
Conclusions
We found a higher prevalence of HH e PH in T2DM outpatients than previously reported due to the finding of compensated PH and mild HH, which can be diagnosed only evaluating gonadotropins and SHBG respectively. We confirmed the known association of HH with BMI, and the correlation of PH with age and creatinine, suggesting different clinical implications for these two forms of hypogonadism and a possible effect of renal function on testicular ageing, or a common cause for organ dysfunction. Finally, the significantly higher prevalence of three years MACEs in HH could suggest this condition as a sign of cardiovascular disease and hints at a possible role of gonadal axis function as a predictive factor in T2DM.

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P68

A Challenging Case of Diabetic Ketoacidosis Due to Thyrotoxicosis

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Purpose
To present a rare case of diabetic ketoacidosis due to thyrotoxicosis and massive pulmonary embolism.
Case presentation
A 40-year-old man from Cameroun, with history of type 2 diabetes treated with gliclazide and metformin, presented with vomiting and abdominal pain. His vital signs were: blood pressure 140/80 mmHg, heart rate 184 beats per minute and temperature 38.2 °C. On admission, laboratory investigation revealed hyperglycemia, hyperosmolality and metabolic acidosis with ketonouria. On examination, the thyroid gland was tender at palpation. Thyroid function tests showed thyrotoxicosis whereas the thyroid ultrasound scan diminished vascularity. Thyroid autoantibodies were negative. The patient was treated with iv fluids, continuous iv infusion of insulin and enoxaparin in prophylactic dose. Alongside, ibuprofen 1800mg daily, propranolol 80mg daily and prednisolone 30mg daily were given as acute thyroiditis treatment. Other causes of ketoacidosis were excluded (negative antibodies for latent autoimmume diadetes of the adult, c peptide: 3.3ng/ml, absent biochemical or clinical signs of infection) which lead to the deduction that the main cause of diabetic ketoacidosis was indeed thyrotoxicosis. During his hospitalization, the patient presented a prefainting episode with hypoxemia and hypotension. The ABGs revealed respiratory alkalosis while the laboratory results showed high levels of d-dimmers and thrombocytopenia. CTPA identified multiple deficits in main and sub-main arterial branches, confirming the diagnosis of massive pulmonary embolism. Since the patient was on prophylactic enoxaparin treatment, heparin induced thrombocytopenia (HIT) was suspected, nevertheless antibody testing was negative. Due to low platelets, thrombolysis was considered unsafe and the patient underwent successful thromboaspiration, with subsequent clinical and hemodynamic improvement. Although the antibodies for HIT were negative the patient was treated with γ-globulin which resulted in gradual platelet increase. All other inherited and acquired coagulation disorders were excluded and no deep vein thrombosis was found. Insulin dose requirements were reduced along with tapering of prednisolone dose. On long term follow up he maintained normal thyroid function and good glycaemic control solely on metformin 1700mg daily and sitagliptin 100mg daily.
Conclusion
Diabetic ketoacidosis is a rare complication in type 2 diabetes patients during acute illness. Thyrotoxicosis due to acute thyroiditis is a rare precipitating factor that should be considered in tachycardic febrile patients with diabetic ketoacidosis. Thyrotoxicosis induced diabetic ketoacidosis can be a highly challenging condition to treat and intensive monitoring is required.

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Effects of Glucagon-Like Peptide-1 Analogs on Sexual Desire: A randomized, double-blind, placebo-controlled crossover trial

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Background
GLP-1 analogs are prescribed for diabetes and obesity due to their well-known insulinotropic, satiation-promoting and appetite-suppressant effects. Several

studies also investigated the effects of GLP-1 analogs on reward to addictive drugs such as alcohol, nicotine and cocaine. Pre-clinical studies suggest that sexual desire, as another type of natural reward, could also be affected by GLP-1 analogs. Since sexuality is a very important aspect of human wellbeing and the use of GLP-1-analogs is becoming more frequent in a broad spectrum of diabetic and obese patients in all age groups, the aim of this study was to investigate the influence of GLP-1-analogs on sexual desire and sex hormones.
Methods
This was a single-center, randomized, double-blind, placebo-controlled, crossover trial conducted at the University Hospital Basel in Switzerland. We enrolled healthy eugonad men of normal weight (BMI 18.5-25kg/m^2 or BMI 25.1-30kg/m^2 and waist circumference $<$102 cm), aged between 18 and 50 years who reported an active and satisfactory sex life. Participants were randomized to dulaglutide and placebo in random order. In the primary analysis, we tested the difference in change in sexual desire, assessed via the Massachusetts General Hospital - Sexual Functioning Questionnaire (MGH-SFQ), after four weeks of treatment with dulaglutide compared to placebo using a paired *t*-test. In secondary analyses, we examined the effect of four weeks of treatment with dulaglutide as compared to placebo on hormones of the reproductive axis (total testosterone, FSH, LH) using paired *t*-tests and adjusted for multiple comparisons using the Bonferroni-Holm procedure.
Results
Between May 2021 and February 2022, 24 out of 26 randomized participants completed the study. The average MGH-SFQ change from baseline after 4 weeks of dulaglutide was 1.0 (SD 2.2) and 0.4 (SD 2.7) under placebo (estimated difference in change of the MGH-SFQ sum score from baseline to end of treatment under dulaglutide and under placebo 0.6 (95% CI: [-0.8-2.0], *P*-value = 0.402). Analyzed hormones of the gonad axis did not show statistically significant differences.
Conclusion
In healthy men, dulaglutide had no clinically relevant effect on sexual desire nor on analyzed hormones of the gonad axis.

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P70

Association between advanced glycation end products (AGEs) and diabetic retinopathy in Latvia

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Background
Diabetic retinopathy is a common complication of diabetes mellitus and the leading cause of blindness in the working-age population in the developed world. Novel biomarkers are needed to improve the screening efficiency for the prevention and early treatment of this condition. Accumulation of advanced glycation end products (AGEs) is considered as one of pathogenetic pathways in development of diabetic complications. AGEs are formed in the process of non-enzymatic glycation of proteins. AGEs assessment could represent a long-term memory of prolonged hyperglycemia and could be an important biomarker in diabetic retinopathy.
Aim
The aim of the current study was to compare AGEs risk groups in patients with different stages of diabetic retinopathy in Latvia.
Methods
Altogether 115 patients with type 1 diabetes and type 2 diabetes were enrolled in the study. Patients were stratified into three groups according to the severity of diabetic retinopathy: "no retinopathy" group; "non-proliferative retinopathy" included patients with mild, moderate and severe non-proliferative retinopathy; group of "proliferative retinopathy" included patients with non-high and high risk proliferative retinopathy and status post laser-photocoagulation. AGEs risk groups (0- normal, 1- mild risk, 2- intermediate risk, 3- high risk) were determined using AGE reader (Diagnoptics). Statistical analysis was performed using programme R: Wilcoxon, Kruskal-Wallis, Fisher, Chi-square test, Kendall's T test and Spearman's correlation.
Results
Subjects in the group of "no retinopathy" (n=57) compared to "non-proliferative retinopathy" (n=29) and "proliferative retinopathy" (n=29) were statistically significantly older, had shorter duration of diabetes, higher prevalence of type 2 diabetes, lower HbA1c and low density lipoprotein levels, less diabetic maculopathy cases. In the group of proliferative retinopathy there was a higher albumin/creatinine ratio in urine. AGEs risk groups were statistically significantly related with the presence and severity of diabetic retinopathy (P=0.000) and also moderately positively correlated with the progression of diabetic retinopathy (Spearman correlation=0.438).
Conclusion
In this study, we demonstrated differences in AGEs risk groups between patients with different stages of diabetic retinopathy in Latvia. AGEs risk group could be used as one of non-invasive biomarkers of diabetic retinopathy.
Acknowledgements
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P71

Protective Role of Matrix Metalloproteinase-2 -1306 C/T and -1575 G/A Gene Polymorphisms Against Type 2 Diabetes Mellitus: A Case Control Study

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Aims
Genetic variations mediating matrix metalloproteinase-2 (MMP-2) expression may result in individual differences in susceptibility to particular diseases. Our aim was to investigate the possible association of certain MMP-2 gene variants with type 2 diabetes mellitus (T2DM) in a Tunisian population.
Subjects and Methods
A case-control study involving 310 normoglycemic control subjects and 791 T2D patients was performed. A total of four MMP-2 SNPs (-1306 C/T; -1575 G/A; -735 C/T and rs9923304 C/T were selected for this study, based on their established minor allele frequency (MAF) $>$5% in Caucasians and association with T2DM comorbidities. Genotyping of MMP-2 variants was performed by real time PCR. Replicated blinded quality control samples were included to evaluate reproducibility of the genotyping procedure; concordance was $>$ 99%.
Results
The MAF of the -1306C/T and the -1575G/A MMP-2, were significantly different between T2DM cases and controls. Setting homozygous wild-type genotype carrier as reference, a reduced risk of T2DM was seen with the -1306C/T and the -1575G/A genotypes. The inheritance hypothesis for this polymorphism was tested according to three genetic models: codominant, dominant, and recessive. According to the dominant model, individuals with GT + TT genotypes of the -1575G/A MMP-2 SNP had a 0.68-fold reduced risk of developing the disease (P=0.012). Moreover, a significant association was shown under the dominant model of the -1306C/T polymorphism with P=0.007 and OR (95% CI) = 0.66 (0.49–0.89), which revealed a 0.66-fold reduced risk within individuals with CT + TT vs individuals with a double homozygote CC genotype. This association persists after controlling for the BMI, total cholesterol and triglyceride covariates as three adjustments models. Haploview analysis revealed limited linkage disequilibrium between the tested MMP-2 and variants, with most haplotypes (99.5%) captured by 7 MMP-2 haplotypes. Taking the GCCC haplotype as reference for MMP-2 (OR=1.00), a reduced frequency of TTCC haplotypes (P=0.04) and the GTCC haplotype (P=3.5x 10^{-5}) was noted in T2D which indicates a protective nature of these two haplotypes for T2D development. Conclusions: To the best of our knowledge, our study is the first to demonstrate the potential of -1306 C/T and -1575 G/A MMP-2 SNPs to reduce the risk of developing type 2 diabetes mellitus.

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Clinical profiling of Acanthosis nigricans in Emirati patients and its association with sex-specific differences in insulin secretion and insulin resistance: a case-control study

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Background
Acanthosis nigricans (AN) is a cutaneous condition characterised by pigmented hyperkeratosis of the skin flexures and neck and occurs most commonly in association with hyperinsulinaemia and insulin resistance (IR). A high prevalence of hyperinsulinaemia and abnormal glucose intolerance has been reported in the Emirati population. Current knowledge of AN suggests that it is a strong visible cutaneous marker associated with IR and can precede the onset of hyperglycaemia. We explored associations of IR, type 1 diabetes (T1DM) and type 2 diabetes (T2DM) with AN (independent of BMI), compared to a control group without AN.
Methods
Case-control study conducted at Imperial College London Diabetes Centre (ICLDC, UAE). Individuals aged <40 years with a clinical diagnosis of AN at <18 years and controls without AN aged <40 years; with or without a diagnosis of diabetes were included. A total of 416 patients, 141 with AN, 275 without AN were recruited. IR was assessed using the Homeostatic Model Assessment of insulin resistance (HOMA2-IR) score.
Results
Mean HOMA2-IR was 0.9, 3.0, 3.6 and 4.2 in individuals with T1DM, NGT, Prediabetes and T2DM, respectively. BMI (OR = 1.13, $P<0.0001$***) and HOMA2-IR (OR = 1.16, $P=0.008$**) were independently and significantly associated with AN. Among individuals with T2DM, HOMA2-IR was significantly higher in association with AN features in women ($P=0.03$*) but not in men ($P=0.23$). Sex-specific differences in associations between AN and HOMA2-B and HOMA2-S were noted. Men with AN demonstrated higher HOMA2-B (OR = 1.01, $P=0.0353$*) than men without AN, while HOMA2-S was significanlty lower in women with AN OR = 0.98, $P=0.0032$**) than without; HOMA2-S in men and HOMA2-B in women were not significantly associated with AN.
Conclusion
This is the first report we are aware of investigating AN and its association with IR, T1DM and T2DM in both males and females in a case-control study in an Emirati population. Awareness and early identification of AN as a clinical marker of IR enables timely recognition of underlying metabolic complications.

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P73

Paediatric Type 2 Diabetes in a single centre in East London in the period 2008-2018

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Objective
Incidence of paediatric type 2 diabetes appears to be increasing. We describe our cohort of paediatric type 2 diabetes at Barts Health NHS Trust in East London (UK) over the period 2008-2018 to gain insight in incidence, complications and outcomes.
Methods
Retrospective cohort study. Data collection from Twinkle (electronic database for diabetes) and paper notes.
Results
Fourty patients (25 female) were diagnosed with T2D at an age of 13.9 ± 1.7 years. Sixty percent were Asian compared to 28% in our T1D cohort. New patients doubled from 2.6/year in 2009-2013 to 5.3/year in 2014-2018. Currently, T2D accounts for 12.5% of our paediatric diabetes cohort. Sixty eight percent had co-morbidities. Learning disabilities were common, more so in males than females (47% vs 16%). At diagnosis, mean BMI was 32.4 ± 6.71 kg/m^2, BMI SDS 2.87 ± 0.70. BMI was 31.7 kg/m^2 for females ($n=23$) and 33.8 kg/m^2 for males ($n=13$) ($P=0.35$). Patients diagnosed in 2014-2018 had higher mean BMI SDS, compared to 2008-2013 (3.06 ± 0.56 vs 2.52 ± 0.81, $P=0.02$) but a lower HbA1c at diagnosis (69.4 ± 19.2 mmol/mol vs 89.0 ± 19.2 mmol/mol, $P=0.02$). BMI and BMI SDS did not change during 2 years follow-up. Mean HbA1c at diagnosis was 75.2 ± 21.0 mmol/mol, decreasing to 55.0 ± 17.4 mmol/mol after 3 months ($P=0.001$) but increasing to 63.0 ± 25.5 mmol/mol at 1 year ($P=0.07$). HbA1c <48 mmol/mol was achieved in 22/37 patients, but only 9/37 patients maintained this for a year, and 2 patients relapsed after this year. Diabetes complications included hypertension ($n=9/21$), dyslipidaemia ($n=9/30$), raised ALT ($n=7/30$), fatty liver ($n=7/24$) and sleep apnoea ($n=6/26$) with similar frequency at diagnosis and during follow-up. Metformin was started in 38/40 patients, 7 patients reduced the dose and 6 stopped due to side effects. 14/37 patients started also on long-acting insulin (0.30 ± 0.16 U/kg), and in 6 combined with prandial insulin (0.42 ± 0.20U/kg). Thirty patients had left paediatrics by 2022, 15 succesfuly transitioned to adult services, 7 were lost to follow up and discharged to their GP, and 4 were discharged to their GP due to diabetes reversal. Mean HbA1c one year after transition ($n=9$) was 70.3 ± 28.2 mmol/mol compared to 74.7 ± 27.6 mmol/mol at transition and 74.7 ± 24.9 mmol/mol at diagnosis.
Conclusion
High burden of co-morbidities and complications is common amongst youth with T2D. Current management does not achieve permanent reduction in BMI or HbA1c, although temporary reduction in HbA1c is achieved in many patients. New treatment approaches are needed to improve outcomes, including strategies for follow-up after transition to adult services.

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P74

Assessment of insulin-releasing and glucose-lowering actions of aqueous extracts of Pterocarpus mildbraedii cellular and diet-induced mice models of type 2 diabetes

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Aim
The use of commonly consumed vegetables, such as *Pterocarpus mildbraedii*, in the treatment of metabolic conditions is consistent with the food-as-medicine strategy. To characterise its pharmacological actions, this study assessed insulin-releasing and glucose lowering effects of effects of *P. mildbraedii* in models of type 2 diabetes.
Methods
Clonal pancreatic cells, BRIN-BD11, were treated *P. mildbraedii* extracts (0 - 0.1-1000μg/ml) in the presence or absence of insulin secretagogues, inhibitors and extracellular calcium. Cytotoxicity and actions of *P. mildbraedii* on cell viability, cell proliferation, intracellular calcium concentration, membrane depolarisation and glucose uptake were assessed together with its *in vivo* actions on diet-induced diabetes.
Results
P. mildbraedii stimulated non-toxic concentration-dependent insulin secretion at all concentrations tested (0.1-1000μg/ml, 1.1-3.4-fold, $P<0.01$-0.001). *P. mildbraedii* extract produced no significant effect on cell viability. Actions of the extract were inhibited by verapamil (50nM, 49%, $P<0.001$), diazoxide (300μM, 50%, $P<0.01$) and absence of calcium (47%, $P<0.01$). Insulinotropic effects increased in incubations containing KCl (30mM, 1.2-fold, $P<0.05$) and different glucose concentration (1.1 to 5.6mM, 1.8-fold, $P<0.01$; 5.6 to 16.7mM, 1.1-fold, $P<0.05$). Enhanced cell proliferation (21%, $P<0.01$), membrane depolarisation (27%, $P<0.05$), intracellular calcium concentration (31%, $P<0.001$), glucose uptake (31%, $P<0.01$) were observed in vitro. Glucose tolerance improved (42%, $P<0.01$) in high-fat fed mice.
Conclusions
These results indicate significant antidiabetic actions of *P. mildbraedii* and suggests the involvement of the ATP-dependent pathway of insulin secretion.

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P75

Acceptability of the switch from parenteral to oral semaglutide in patients with type 2 diabetes mellitus and obesity: Patient satisfaction, and changes in HbA1c, body weight, systolic blood pressure and tryglicerides

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Introduction
During most of the autumn of 2022, the standard maintenance presentation of parenteral semaglutide (1.0 mg for weekly dosage) was temporarily unavailable. Many of the patients using this dose were switched to the standard maintenance dose of oral semaglutide (14 mg daily). The leaflet included with the product specifies that the 14 mg daily oral dose is equivalent to the 0.5 mg parenteral weekly dose, but this is most likely an interpolation, as there are no reported head-to-head comparisons of the comercially available doses of oral and parenteral semaglutide in the literature.
Methods
We obtained data retrospectively from patients with obesity and type 2 diabetes who had switched from 1.0 mg parenteral semaglutide to 14 mg oral, forced by the unavailability of the parenteral presentation. Body weight, BMI, SBP, HbA1c, triglycerides and reported side effects were obtained from the clinical records. The patients answered anonymally a simple web-based questionnaire with two questions: -Their satisfaction with the switch from parenteral to oral semaglutide was: [very high/high/fair/low/very low/no answer]. -Would they switch back to parenteral semaglutide when available [yes/no/no answer]. All patients included gave their informed consent.
Results
48 patients who had been at least 3 months with parenteral semaglutide 1.0 mg weekly and switched to oral semaglutide 14 mg daily were recruited, with available data in the last month before the switch and new data 2-4 months after the switch. 26 (54%) were female, mean $\pm$ sd age was 57 $\pm$ 13 years, and diabetes duration vas 8.4 $\pm$ 6.2 years. There was a non-significant reduction in BMI (-0.3 $\pm$ 0.2 kg/m^2), in HbA1c (-0.41 $\pm$ 0.25%), in SBP (-4 $\pm$ 2 mmHg) and a non-significant increase in triglycerides (+16 $\pm$ 12 mg/dl). 7 (15%) of the patients reported new or worsened minor gastrointestinal side effects but there were no withdrawals. Reported satisfaction with the switch was 16/18/15/4/0/1 [very high/high/fair/low/very low/no answer]. The intention to switch back was 18/29/1 [yes/no/no answer].
Conclusions
In this group of patients with obesity and type 2 diabetes we did not find inferior results with oral semaglutide 14 mg daily vs. parenteral semaglutide 1 mg weekly. A solid majority of the patients (70%) reported high or very high satisfaction with the switch, and 62% had no intention of switching back. The reported side effects of the switch were infrequent and minor. We conclude that the acceptability of switching parenteral to oral semaglutide was high in our patients, with no apparent inferiority in clinical results.

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P76

Very-low-calorie-ketogenic-diet (VLCKD) as a nutritional therapeutical option for chronic management in obese patients with type 2 diabetes: a case report

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Introduction
It is known that very-low-calorie-ketogenic-diet (VLCKD) has beneficial effects on body weight in overweight diabetic patients. Adopting this diet with artificial meals or natural foods in type 2 diabetes (T2DM) has been largely studied, and conflicting results have been reported regarding its effects on glycemic profiles, dyslipidemia, and liver function. In fact, the high level of fat content in natural foods could have a negative impact on hepatic steatosis, and high protein content in artificial meals may affect renal function.
Case
We describe a 62-year-old female patient with T2DM complicated by diabetic nephropathy who underwent a VLCKD. When T2DM was diagnosed in 2010, her glycated hemoglobin (HbA1c) was 61 mmol/mol and body mass index (BMI) was 37.1 kg/m^2. She also had dyslipidemia and severe hepatic steatosis. She was initially managed with metformin and a Mediterranean diet with an improvement in glycemic control and discrete weight loss (HbA1c 49 mmol/mol, BMI 34.8 kg/m^2). Three years later, she presented poor glycemic control (HbA1c 65 mmol/mol), regain of body weight and diabetic nephropathy appeared (estimated glomerular filtration rate, eGFR, 49 ml/min/1.73m^2, albuminuria 266 mg/l). Therefore, metformin was discontinued, basal insulin therapy was started, and liraglutide (until 1.8 mg/day) was added to improve weight loss. Metabolic control improved quickly and remained stable over time, but she only had minimal weight loss (BMI from 35.5 to 35.1 kg/m2 in four years despite therapy). Therefore, in August 2019, she was advised to start a VLCKD. Just one month after, she had a remarkable improvement in glycemic control, so she discontinued all therapy. After six months of diet, not only the excellent glycemic control (HbA1c 37 mmol/mol) persisted, but there were also an important weight loss (BMI 29.9 kg/m2), together with amelioration of dyslipidemia, hepatic steatosis, and diabetic nephropathy (eGFR 61.5 ml/min/1.73m^2, albuminuria 1.6 mg/l). In February 2020, VLCKD was replaced by a low-calorie-diet followed for one year, in which she had partial weight gain and worsening renal function. Then, she switched a low-carbohydrate-diet and all parameters improved again.
Discussion
The best dietary approach in subjects with T2DM remains debated. However, in literature, it has been suggested that not only VLCKD seems to be safe and effective in obese diabetic patients with impaired renal function and liver disease, but that it may even help significantly improving both, as in this case.

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P77

En route to sarcopenia biomarkers: dp-ucMGP in relation to muscle mass and function

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Sarcopenia is characterized by progressive loss of both mass and function of skeletal muscle when ageing. It poses a serious issue for healthcare systems, as it is associated with increased risk of falls, osteoporosis, and mortality. To date, no ideal serum biomarkers for the diagnosis of this complex condition have been identified. Matrix-GLA-protein (MGP), primarily known as a vitamin K dependent calcification inhibitor, is present and active in bone, muscle, and adipose tissue. It acts as an adipokine and has been linked to reduced muscle strength. Therefore, its dephosphorylated and uncarboxylated isoform (dp-ucMGP) was investigated as a potential biomarker in sarcopenia. To find associations of dp-ucMGP and sarcopenia related parameters, data from the BioPersMed cohort ("Biomarkers for Personalized Medicine") were analyzed. The cohort included 1022 asymptomatic volunteers (58 $\pm$ 9 years) at moderate cardiovascular risk. In 760 persons, serum measurements of dp-ucMGP were analyzed with the InaKtif MGP Kit using the IDS-iSYS Multi-Discipline Automated System. Body composition was measured by Lunar iDXA and clinical and physical performance data were collected. Several sarcopenia definitions were used, based on either muscle mass (appendicular muscle mass [ASM] or appendicular muscle mass index [AMMI]) or muscle function (handgrip strength [HGS] or 400m walk test). Dp-ucMGP plasma levels correlated negatively with gait speed (Spearman's rho [ρ] = 0.192; $P < 0.001$). Using gait speed for defining groups, serum levels were higher in the sarcopenia compared to the non-sarcopenia group (716 $\pm$ 306.6 vs. 491 $\pm$ 164.4 pmol/l; $P = 0.006$). The highest dp-ucMGP quartile also showed the highest risk of reduced HGS, another marker of physical performance (Odds ratio [OR] = 3.688; 95% CI 1.007 - 13.502). Other than with muscle function, dp-ucMGP showed a positive correlation to the muscle mass parameters AMS ($\rho = 1.102$; $P = 0.005$) and AMMI ($\rho = 0.122$; $P = 0.001$). Serum levels were lower in persons with sarcopenia than without, using both ASM and AMMI for defining groups ($P < 0.001$ and $P = 0.012$, respectively). The lowest dp-ucMGP quartile had the highest risk for reduced muscle mass (i.e., AMMI), decreasing with each quartile. In sum, dp-ucMGP plasma levels are lower in sarcopenia defined by muscle mass (i.e., ASM and AMMI), but higher in sarcopenia defined by muscle function (i.e., HGS and gait speed). Serum dp-ucMGP can be considered as a potential biomarker candidate for characterizing sarcopenia and may be a promising link between bone, fat, and muscle.

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P78

Epicardial Fat, a cardiovascular risk factor with implications in kidney function

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Aim
Epicardial adipose tissue (EAT) has important physiologic functions, nonetheless, excessive EAT leads to a proinflammatory state with adverse effects on the myocardium. EAT has also been associated with adverse outcomes in chronic kidney disease (CKD) patients. We think that visceral adipose tissue (VAT) and organ-specific ectopic fat plays an important role in cardiorenal dysfunction. The aim of our study is to analyse the relationship between EAT and the risk of developing albuminuria.
Methods
We reviewed the records of subjects who underwent a routine health check-up, had a computed tomography whole body scan and blood test in the same visit at our Center from July 1, 2003 to December 31, 2006 and had at least one follow-up control (181 patients were included in the analysis). EAT was quantified semiautomatically including voxels with attenuation values between -45 to -190 HU. EAT was adjusted for body surface area (EATi; normal limit: 68.1 cm^3/m^2). The outcome was defined as the presence of albuminuria at follow-up. Micro-albuminuria and macro-albuminuria were defined as urinary albumin-creatinine ratio (UACR) >30 mg/gCr and >300 mg/gCr in spot urines, respectively.
Results
Mean age was 55.9 ± 8.5 years (76.8% were men). Seventy-seven (43%) subjects had normal EATi and 104 (57%) an abnormal EATi. Patients with abnormal EATi were predominantly men, older and had a higher glycemia, HOMA-IR, a more detrimental lipid profile, hyperuricemia, worse liver function ($P<0.05$), a higher prevalence of metabolic syndrome disorders, higher indices of adiposity and higher CAC Score. We observed a 36.5% (95% CI: 20.2-52.8), 54.3% (95% CI: 42.7-65.8) and 85.3% (95% CI: 73.0-97.6) of subjects with abnormal EATi in each tertile of VAT, respectively. The proportion of subjects with abnormal EATi was significantly higher at the third tertile of VAT compared with the first tertile (diff: 49% 95% CI: 25% - 72%) ($P<0.01$). After a median follow up of 11.22 years (25th percentile: 4.7; 75th percentile: 14.9), 32 events of albuminuria were registered. Mean (sd) albuminuria of those subjects was 242 mg/gCr (769.13). Patients with high levels of EATi had an increased risk of albuminuria after adjustment for age, sex, BMI, diabetes and antiplatelet therapy, medical treatment for diabetes, dyslipidemia, hypertension, or hyperuricemia at baseline using the IPW method: HR (95% CI) 4.05 (1.19-13.82) ($P=0.025$).
Conclusions
EAT is associated with renal dysfunction assessed through urinary albumin-creatinine ratio. Our results, endorse the term Obesity-related Adipose tissue Disease (OrAD) to collectively englobe the diverse pathologies related to adiposopathy.

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P79

Central Actions of Leptin Sensitizer Celastrol

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Celastrol, a triterpene compound derived from the thunder god vine (Tripterygium wilfordii), has shown promising efficacy in preclinical models for the management of metabolic disorders such as obesity and diabetes. The compound exhibits anti-inflammatory properties and has been shown to enhance insulin sensitivity and modulate lipid metabolism. The observed weight loss effects are thought to be primarily mediated by its ability to augment leptin sensitivity. Despite extensive research, its exact mode of action remains poorly understood. We and others suggested that the therapeutic effects of celastrol may, to a large extent, be mediated by the hypothalamus and its neural circuits that control food intake and appetite. However, no studies to date had explored the direct metabolic effects of celastrol after central application. In this study, we aimed to specifically examine whether centrally administered celastrol can regulate energy and glucose metabolism in rodents. Using mice, we show that the subchronic treatment with intracerebroventricular (icv) 3 celastrol improves sensitivity to leptin in animals that were fed a high-fat diet. By hyperinsulinemic-euglycemic clamp measurements we further demonstrate that rats fed a high-fat diet exhibit improved glucose metabolism when acutely infused with icv 3 celastrol. In order to determine cellular targets mediating these effects, we employed single nucleus RNA sequencing of hypothalamic leptin receptor-expressing cells. We reveal dramatic transcriptional effects of celastrol in a leptin resistant state of diet-induced obese mice as well as the transcriptional signature of leptin together with a celastrol pre-treatment. Our results suggest a previously unappreciated weight loss-independent mechanism of action of celastrol in the regulation of glucose homeostasis and new insights for potential molecular targets in the treatment of obesity and leptin resistance.

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P80

Cardiac Autonomic Regulation and Metabolic Syndrome: Clinical Use of A Unitary Autonomic Nervous System Index

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Background
Metabolic syndrome (MetS) represents a huge public health problem worldwide, being associated with an increased risk of cardiovascular and oncological diseases, and all-cause mortality. There is compelling evidence supporting a key role of dysfunctional autonomic nervous system (ANS) in such an association as well as the mutual correlation between the components of MetS. Autonomic Nervous System Index (ANSI) is a percent ranked (0–100) unitary proxy of cardiac autonomic regulation (CAR), extracted from the autoregressive spectral analysis of heart rate variability (HRV) by combining the three most informative indexes. It is a simple and non-invasive method to evaluate and monitor ANS function, being by design free of age and gender bias [1].
Aims
To investigate CAR by means of ANSI in patients affected with MetS.
Methods
133 patients referred to the Exercise Medicine Clinic of Istituto Auxologico IRCCS underwent assessment of CAR - by means of ANSI - alongside lifestyle with ad hoc questionnaires focusing on weekly physical activity volume, nutrition quality, and perception of stress, fatigue and somatic symptoms. Participants were retrospectively subdivided into two groups according to the presence or not of MetS criteria (established by the Joint Interim Statement in 2009 [2]).
Results
58 subjects were affected with MetS, while 75 were not (non-MetS). Non-MetS patients were characterized by a significant prevalence of females and lower age as compared with MetS counterpart. ANSI (free of age and gender bias) was significantly impaired (32.9 vs 44.8, $P=0.007$) in MetS subset. No significant differences were found in terms of lifestyle between the groups.
Conclusions
This is the first study assessing CAR by means of ANSI in MetS patients. Such findings indicate neurovegetative dysregulation in MetS. Intriguingly, in view of the increased cardiovascular risk mediated via - among others – ANS impairment in MetS, early screening for ANS dysfunction with simple but reliable methods may be clinically advantageous, with a view to undertaking and monitoring therapeutic strategies that aim to restore autonomic balance (e.g., personalized lifestyle management programs).
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P81

Early impact of bariatric surgery on obesity-related kidney dysfunction

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Background

Renal dysfunction is known to be more prevalent amongst patients with obesity. Metabolic and bariatric surgery is associated with positive renal effects through intricate pathways. We aimed to determine the short-term impact of laparoscopic sleeve gastrectomy (LSG) on renal function and to identify parameters associated with its variation.

Materials and methods

We performed a retrospective study on 268 patients (115 males and 153 females) evaluated before and six months after LSG. Clinical and anthropometrical data were collected, as well as an extensive biological panel and body composition assessment using whole-body dual-energy X-ray absorptiometry (DXA). CKD-Epi (2021) formula was used to estimate glomerular filtration rate (eGFR) both pre- and postoperatively.

Results

Mean baseline BMI was 44.25 kg/m^2 ($\pm$ 6.17 kg/m^2) and mean 6 months excess weight loss percentage (EWL) was 70.04% ($\pm$17,38%). Diabetes mellitus (DM) and hypertension had a prevalence of 18.3 and 50% respectively. Mean eGFR (ml/min/1.73 m^2) was 87,68 (15.92), with a cumulative prevalence of mild and moderate renal dysfunction of 55.2%. The prevalence of renal hyperfiltration was surprisingly low (0.7%). Six months postoperatively, mean eGFR increased to 93.23 ($P<0.001$) and the prevalence of renal dysfunction decreased to 40.7%. Interestingly, this improvement correlated with EWL (rho = -0.307, $P=0.001$), total lean mass (rho = -0.257, $P=0.012$) and appendicular skeletal muscle mass index (ASMI; rho = -0.264, $P=0.01$) variations in males, as opposed to total visceral adipose tissue (VAT) mass (rho = -0.235, $P=0.01$) and LDL cholesterol (rho = -0.187, $P=0.02$) variations in females. Of these, EWL, VAT mass and LDL cholesterol variations were independent predictors in a model adjusted for the remission of either hypertension or DM.

Discussion and conclusions

Our results are in line with previous findings on the positive impact of LSG on renal function. Hyperfiltration is thought to be associated with early stages of obesity-related glomerulopathy and its low prevalence suggests delayed presentation in our cohort. The identified differences might point to gender-specific drivers of kidney dysfunction associated with obesity and its resolution. Specifically, visceral adiposity seems to play a more prominent role in females. If confirmed by further studies, this could aid in the optimization of medical treatment.

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P82

Testosterone serum levels predict the severity of metabolic dysfunction associated fatty liver disease (MAFLD) in hypogonadal men

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Background

Metabolic dysfunction associated fatty liver disease (MAFLD), the leading cause of chronic liver disease, is defined as the presence of hepatic steatosis and metabolic risk factors. Both testosterone and estradiol seem to have a pivotal role in hepatic lipid homeostasis, although underlying mechanisms are still unclear. Low testosterone serum levels result independently associated with MAFLD, but no studies so far evaluated MAFLD prevalence and severity in hypogonadal men.

Aim of the study

To evaluate MAFLD prevalence and severity in a cohort of hypogonadal men.

Methods

A prospective, observational, clinical trial was conducted enrolling hypogonadal men (testosterone serum levels <3 ng/ml) and collecting medical history, anthropometrical characteristics, hormonal (testosterone, estradiol, sex hormone binding globulin [SHBG] and prolactin) and biochemical (liver enzymes, lipid profile, glycemia and glycated haemoglobin) parameters. Each patient underwent hepatic ultrasound to evaluate the presence and grade of steatosis, and Fibroscan® and 2-dimensional shear weave elastography (2D-SWE) techniques for the assessment of liver stiffness. A liver stiffness $\pm$ 8 kPa was considered diagnostic for liver fibrosis.

Results

Twenty-six hypogonadal men (age 59.9 $\pm$ 13.8 years, body mass index 33.9 $\pm$ 7.4 kg/m^2) were enrolled, of which 20 (76.9%) presented secondary hypogonadism, and six (23.1%) a primary form. Eighteen patients (69.2%) were already under androgen replacement therapy (mean treatment duration 4.5 $\pm$ 3.7 years), presenting mean testosterone serum levels above the lower level of the reference range (3.9 $\pm$ 2.9 ng/ml). Hepatic steatosis was detected in 16 patients (61.5%), divided into mild (7.7%), moderate (26.9%) and severe (26.9%) grades. No difference in liver steatosis presence/grade was detected between androgen-replaced patients compared to untreated ones. Liver stiffness was 6.8 $\pm$ 5.4 KPa (IQR 16.2 $\pm$ 7.1%) at Fibroscan® and 7.7 $\pm$ 10.3 KPa (IQR/M 21.5 $\pm$ 8.1%) at 2D-SWE. Liver fibrosis was detected in five men (19.2%) at Fibroscan® and in 4 (15.4%) at 2D-SWE. The presence of liver fibrosis according to both elastography techniques was not associated to any biochemical parameter. However, multivariate analysis showed that liver stiffness was predicted by alanine transaminase (ALT) (B: 0.780, $P<0.005$) and testosterone (B: -1.819, $P=0.022$) serum levels.

Discussion

Here, we demonstrated a high prevalence of liver steatosis in hypogonadal men, especially of moderate/severe grades. Moreover, using different elastography techniques, we highlighted an unexpectedly high prevalence of liver fibrosis, occurring in more than 15% of cases. Although our results need further confirmation in larger cohorts, the inverse correlation between liver stiffness and testosterone serum levels at least suggests the need to assess the presence of MAFLD in hypogonadal patients.

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Understanding the cultural fit of the REDE model for physician-based communication skills training: A focus group discussion with South Indian patients with T2DM

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Background

In India, physicians recognise the need for communication skills training (CST) so as to improve patients' physical and mental wellbeing. Yet, there is a lack of culturally informed and evidence-based training programs in the current medical curriculum. In our pilot study, we explored the cultural suitability of the Relationship: Establishment, Development and Engagement (REDE) model for CST for Indian physicians. The REDE model proposes three ways (i.e., establishing, developing and engaging) for physicians to foster a meaningful interaction and, subsequently, relationship with patients. Our pilot study supported the appropriateness of the REDE model of communication for Indian physicians. Therefore, using a larger sample representing mainly South Indians, the current study aimed at understanding patients' experience and expectations using the framework of the REDE model.

Aim

(1) To document the experiences and expectations of communication from one's treating physician among South Indian patients with type 2 diabetes mellitus (T2DM) and (2) to understand the cultural fit of the REDE model to train Indian physicians in communication skills.

Methods

Using convenient sampling, 61 patients (mean age = 52.19 years) with T2DM were recruited for the study from 5 cities in South India (Hyderabad = 12,

Chennai = 11, Bengaluru = 09, Trivandrum = 18, Mumbai = 11). Eight recorded focus group discussions were carried out virtually, exploring patients' thoughts, feelings, needs and efforts towards establishing a communicative relationship with their physician. The data were analysed using conventional content analysis.
Results
Three themes were constructed: (1) *"A friendly nature in conversations helps in treatment*': Essential skills in establishing a relationship with a patient, (2) "*Respond well and listen more*': The bridge to developing a long-lasting meaningful relationship, and (3) a desire for a conversation balanced with technical details and a thoughtful, sensitive and empathic approach.
Discussion & Conclusion
This study underscores the need to introduce a CST program to engender physicians' ability to build strong, meaningful, and enduring relationships with their patients. In particular, the findings suggested a shift in Indian patients' preference for a collaborative and empathic relationship with their physician than the previously accepted authoritative/paternalistic model of care. Further, the study findings support the cultural fit of all the three components of the REDE model to develop a CST for Indian physicians treating patients with T2DM. These findings will aid in developing a REDE-model based CST program for Indian physicians' treating patients with T2DM.
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Glycemic variability in type 1 diabetics treated with human insulin
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Introduction
Type 1 diabetes is an endocrinopathy due to insulin deficiency. Its treatment consists in administering an exogenous insulin simulating the physiological secretion. The objective of this study was to evaluate glycemic variability in a group of adolescents with type 1 diabetes treated with human insulin.
Method
This is a cross-sectional study, including type1 diabetic patients treated with human insulin, who underwent continuous glucose monitoring (CGM) for 6 days. We analyzed the CGM data for each patient and we calculated the coefficient of variability of glucose (CV), mean of glycemic excursions (MAGE) and the mean of daily differences (MODD). The Time Above Range (TAR) defined as >180 mg/dl, the Time Below Range (TBR) defined as <70 and <54 mg/dl and the Time In Range (TIR) were derived From CGM.
Results
We included 36 patients with type 1 diabetes with an average age of 17 ± 1.8 years old. Nineteen patients were female and seventeen were male. The average duration of diabetes was $6.6\pm$ 4.6 years. The average total insulin dose was 55.6 $\pm$ 18 UI (0.92 ± 0.31UI/Kg), the average total dose of rapid insulin was 20 $\pm$ 8 UI ($0.33\pm$ 0.12 UI/Kg) and that of basal insulin was 35 ± 12UI (0.6 ± 0.22UI/Kg) . The average CV was 38 ±11%, and more than half of the patients (58.3%) had a coefficient of variability greater than 36%. In addition, the mean MAGE was 141 ± 46 mg/dl and only 2 patients had a MAGE $\leq$ 65 mg /dl. Furthermore, the average MODD was 91 ± 42 mg/dl and 77.8% of patients had MODD ≥60 mg/dl. Time in range varied from 4 to 88% with an average of 37 ± 19%. Time below range varied from 0% to 36% with an average of 7 ± 9%. The mean of time above range was 55 ± 23%. TIR was negatively correlated with total insulin dose ($r=$-0.41, $P=0{,}013$). TAR was positively correlated with the dose of rapid insulin ($r=0{,}34$ $P=0{,}039$). The dose of rapid insulin was positively correlated with TAR ($r=0{,}34$ $P=0{,}039$) and negatively correlated with TIR ($r=$-0.47 $P=0{,}004$).
Conclusion
In our study we concluded that the majority of patients are overdosed in basal insulin and have high glycemic variability.
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Depressive Symptoms in Patients With Type 1 and Type 2 Diabetes: prevalence and associated factors
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Background and Aim
Patients with type1 and type2 diabetes both have a high prevalence of depressive symptoms. The aim of this study was to evaluate the prevalence of depressive symptoms and associated factors in patients with diabetes.
Methods
This is a cross-sectional study conducted in 140 patients with diabetes. Patients' demographic characteristics, current treatments, glycemic control, cardiovascular risk factors, diabetes-related complications were collected. Treatment adherence was evaluated by Medication Adherence Questionnaire (MAQR) of Morisky-Green. Tobacco dependence was evaluated by the Mini fagerstrom test. Patients were asked to complete the 9-item Patient Health Questionnaire(PHQ-9)to evaluate depressive symptoms. Total PHQ-9 score ranges from 0 to 27. In this study, we combined scores10–27 ("moderately severe or severe") to improve precision of estimates. We defined PHQ-9 total scores ≥10 as clinically relevant depression(CRD)[1].
Results
Of the study population, mean age was 54.88 ± 12.97 years with female predominance (55.6%),87.3% of patients had type 2 diabetes. Mean diabetes duration was 13.43 ± 7.3 years, mean glycated hemoglobin was 9.7% ±1.76 and mean BMI was $28.3\pm$ 7.5Kg/m^2. Among the subgroup of type 2 diabetes patients,20.4% of patients used oral glucose-lowering drugs(OGLDs) only, and 79.6% used OGLDs plus insulin, In the whole population study,70.5% reported depressive symptoms(PHQ-9 score$\geqslant5$) and 36% had CRD. CRD was significantly associated with female sex (70%vs46,1%; $P=0{,}007$), high tobacco dependance (100% vs 57%; $P=0{,}01$) and poor treatment adherence (54% vs 36 %; $P=0{,}03$). Patients with CRD had higher total cholesterol (4.67 ± 1.22 mmol/l vs $4.14\pm$ 0.98 mmol/l; $P=0.008$), higher HDLc($1.31\pm$ 0.59 mmol/l vs 1.12 $\pm$ 0.27mmol/l; $P=0{,}012$) and higher LDLc(1.06 ± 0.35 vs 0.91 ± 0.3mmol/l; $P=0.015$). Diabetes treatment, type of diabetes, microvascular and macrovascular complications did not statisticcaly differ between the two groups.
Conclusion
Depressive symptoms are common in patients with diabetes calling for routine screening to reduce the double burden of diabetes and depression and their negative interaction.
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IADPSG Vs Carpenter and Coustan Criteria for the Diagnosis of Gestational Diabetes Mellitus in a Spanish Population: Is it Worth Switching?
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Objective
The aim of this study was to evaluate maternal and perinatal outcomes before and after implementation of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria for testing of gestational diabetes mellitus (GDM).
Methods
This is a retrospective cohort study of women with GDM followed at a single university hospital. We compared maternal and neonatal outcomes of singleton pregnancies in women with GMD before (from January to December 2014) and after (from January to December 2016) the introduction of IADPSG criteria for the diagnosis of GDM. The same therapeutic interventions were offered to women with GDM diagnosed by both criteria.
Results
Use of IADPSG compared to Carpenter and Coustan (C& C) criteria increased the rate of women diagnosed with GDM (6.4% vs 11.9%, $P=0.001$). The IADPSG group had a lower rate of small for gestational age (14.8 vs 4.8%, $P=0.001$), but there were no differences in cesarean delivery rate (22.9 vs 22.9 %, $P=0.988$), instrumental delivery rate (11.4 vs 9.5%, $P=0.542$), large for gestational age rate (17.0 vs 20.6 %; $P=0.404$), and neonatal intensive care unit admission rate (15.6 vs 11.4%, $P=0.244$). Insulin use was similar in both groups (45.8 vs 43.0%, $P=0.115$), but a basal-bolus regimen was used more frequently in the C& C group (13.6 vs 7.0%, $P=0.031$). There were no significant differences in any other pregnancy outcomes. To better characterize the differences in the rate of SGA, we analyzed maternal and neonatal outcomes stratifying the IADPSG group according to whether women were diagnosed by FPG in the first trimester (FPG-IADPSG group) or by 75 g OGGT in the second trimester (OGGT-IADPSG group). There were no significant differences in the rates of maternal and neonatal outcomes among the three groups except for SGA, which remained more frequent in the C& C group than in the FPG-IADPSG and OGTT-IADPSG groups (14.0% vs 4.8% vs 4.4%, respectively; $P=0.006$). Only the C& C screening (OR 3.76, 95% CI 1.65-8.57), and smoking habit (OR 3.31, 95% CI 1.44-7.59) were associated with SGA in the multivariate logistic regression model to evaluate predictors of this outcome.
Conclusion
Except for a decrease in the rate of small for gestational age, adopting the IADPSG criteria was associated with more GDM diagnoses without better maternal and neonatal outcomes.

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Substantial Burden Associated With Hyperphagia and Obesity in Children With Bardet-Biedl Syndrome

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Background
Bardet-Biedl syndrome (BBS) is a rare melanocortin-4 receptor (MC4R) pathway disease characterized by early-onset, severe obesity and hyperphagia associated with primary cilia dysfunction. Patients with rare MC4R pathway diseases of obesity and hyperphagia, including BBS, experience high disease burden, but the relationship between hyperphagia and body weight in patients with BBS is not fully understood. We assessed the correlation between hyperphagia score and obesity in children with BBS.
Methods
Data (2014-2021) from CRIBBS, an international registry of patients with BBS, were analyzed. For children who had $\geq$4 weight assessments, the degree of hyperphagia was derived from the Hyperphagia Questionnaire completed by the caregiver 4 years after CRIBBS recruitment. Hyperphagia Questionnaire scores range from 11 to 55, with higher values indicating more severe hyperphagia. Body weight was measured yearly. Average Hyperphagia Questionnaire scores by weight category (ie, obese, body mass index [BMI] $>$95th percentile; overweight, BMI $\geq$85th and $<$95th percentiles) and the correlation between Hyperphagia Questionnaire score and BMI percentile are reported.
Results
Of 107 eligible children, 39 had the Hyperphagia Questionnaire completed by their caregiver at Year 4 and were included in the analyses. At the time of the hyperphagia assessment, the mean age was 10.4 (range, 4 to 17) years, and 56.4% were male. The mean Hyperphagia Questionnaire score was 24.1 (median, 26.0; range, 11.0 to 39.0). The mean Hyperphagia Questionnaire score increased by weight category, from 13.0 [median, 12.0] among the 5 children (12.8%) with weight within the reference range/underweight to 22.8 [median, 24.0] among the 5 children (12.8%) with overweight and to 26.2 [median, 26.0] among the 29 children (74.4%) with obesity. The Hyperphagia Questionnaire score and BMI percentile were positively and significantly correlated ($r=0.34$; $P=0.03$).
Conclusions
Children with BBS experienced burden due to hyperphagia, which was correlated with obesity, suggesting that treatments impacting hyperphagia may result in weight loss and quality of life improvements in these children.

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Indications that the vitamin D-endocrine system is altered in obese people

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Background
In obese patients compared to non-obese subjects, serum immunoreactive parathyroid hormone (PTH) is higher and decreases with weight loss.
Objectives
To find out if obesity affects the vitamin D endocrine system and if the resulting secondary hyperparathyroidism is linked to a decrease in urine calcium.
Material and Methods
25 healthy individuals were examined. Between the ages of 21-30 years, there were 13 obese people and 12 non-obese subjects. They were only allowed to consume purified water and were fed a steady diet of 300 mg of calcium, 800 mg of phosphorus, 15 meq of magnesium, 100 meq of sodium, and 60 meq of potassium each day. For the analysis of serum calcium, ionized calcium, phosphorus, magnesium, creatinine, Gla protein, 25-hydroxyvitamin D, 1,25-dihydroxy vitamin D, and immune-reactive PTH, fasting blood samples were taken. Calcium, phosphorus, salt, potassium, magnesium, creatinine, and cyclic AMP were measured in 24-hour urine samples.
Results
Those who were obese weighed an average of 105 ± 5 kg, compared to non-obese (67 ± 1 kg; $P<0.02$).. While mean serum calcium, mean serum ionized calcium, and mean serum phosphorus were similar between the two groups, mean serum immunoreactive PTH (517 ± 47 vs. 242 ± 32 pg/ml, $P<0.002$), mean serum 1,25 dihydroxy vitamin D (36 ± 1 vs. 29 ± 1 ng/ml, $P<0.02$), and mean serum Gla protein (32 ± 1 vs. 22 ± 2 ng/ml, $P<0.02$) were significantly higher. Mean blood 25-hydroxyvitamin D levels were substantially lower in obese men and women than in nonobese individuals (7 ± 2 s. vs. 21 ± 1% ng/ml, $P<0.002$). Mean urine phosphorus was the same in both groups, however mean urinary calcium was considerably lower in the obese group (114 ± 11 mg/d vs. 165 ± 12 mg/d, $P<0.02$) and had higher mean urinary cyclic AMP (3.17 ± 0.42 mg/dl vs. 1.83 ± 0.24 mg/dl GF, $P<0.02$) and creatinine clearance (215 ± 12 mg/d vs. 172 ± 5 mg/d, $P<0.02$). Both urine cyclic AMP and serum immunoreactive PTH were significantly correlated with percentage of ideal body weight ($r=0.523$, $P<0.02$) and the percentage of ideal body weight ($r=0.715$, $P<0.02$), respectively.
Conclusion
Secondary hyperparathyroidism is linked to greater renal tubular reabsorption of calcium and elevated levels of circulating 1,25(OH)2D, is a feature of the vitamin D endocrine system change seen in obese people. They have lower levels of serum 25-OHD due to feedback regulation of the precursor's synthesis in the liver brought on by higher levels of serum 1,25(OH)2D.

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Does intermittent fasting improves metabolic and inflammatory parameters in obeseadult ?

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Introduction
During these last years, Intermittent fasting was emerging as an approach that improves weight and metabolic outcomes in obese subjects.
Objective
To investigate the effects of 16:8 intermittent fasting on metabolic and inflammatory parameters in adult obese.

Methods
This is a comparative interventional study conducted in 60 obese women consulting the obesity unit of the Institute of Nutrition of Tunis during the period ranging from May to August 2022. The patients were divided into 2 groups matched for age and sex. G1: standard hypocaloric diet and G2: intermittent fasting 16:8. Anthropometric measurements and biological parameters were taken at T0 and T1 (3 months after the dietary intervention).
Results
The mean age was 35.81 ± 8.92 years. Decreases in weight ($P = 0.005$) and Waist circumference ($P < 10\text{-}3$) were significantly greater in patients on the 16:8 IF compared with those on the standard hypocaloric diet. Patients who adhered to intermittent fasting had a greater decrease in fasting blood glucose with a significant difference between the two groups ($P = 0.003$), HbA1c ($P = 0.006$), insulin levels ($P = 0.003$), insulin resistance ($P < 10\text{-}3$), uric acid ($P = 0.010$) compared to patients in the hypocaloric diet group. The variation in lipid parameters was not significant between the two groups. Except for a statistically significant increase in HDL-c in group 2 ($P = 0.001$). The variation in IL-6 concentration was +0.06 and -0.26 pg/ml respectively for the low-calorie diet group and the intermittent fasting group with $P = 0.007$. No significant variation in TNFα levels was observed afterthe two type of diets.
Conclusion
The results of this study suggest that intermittent fasting is a feasible and effective acceptable dietary model for the management of obese women.

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Vitamin D supplementation reduces oxidative stress caused by hyperuricemia in type 2 diabetes mellitus patients

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Introduction
It is suggested that hyperuricemia in type 2 diabetes (T2DM) patients causes reactive oxygen species (ROS) accumulation, which causes the destruction of beta cells of the pancreas and contributes to T2DM. This study aimed to analyze the relationship between vitamin D deficiency (which is reciprocally related to Serum Uric Acid (SUA) levels), hyperuricemia, and levels of ROS scavengers in T2DM patients, and to investigate the effect of vitamin D supplementation on these parameters.
Materiel & Methods
The study included 26 T2DM patients with vitamin D deficiency who received vitamin D supplements for three months. HbA1c, insulin, SUA, xanthine oxidase (XO) levels, lipid peroxidation, Glutathione Peroxidase (GPx) activity, GSH/GSSG ratio, and vitamin D levels were measured prior to and after supplementation.
Results
Adenosine deaminase (ADA) and XO levels and activity were elevated in T2DM patients, along with SUA levels. Vitamin D supplementation resulted in significant (P value $< .005$) decreases in HbA1c, HOMA-IR, SUA, XO levels, ADA levels, and activity, lipid peroxidation, and GPx activity. A significant increase in GSH/GSSG ratio was also observed.
Conclusion
Vitamin D supplementation reduces oxidative stress caused by high levels of uric acid observed in T2DM patients by reducing the activity of ADA and XO enzymes.

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A study to evaluate clinical and metabolic profile in a type 1 diabetes cohort receiving dpp4 inhibitor plus SGLT2 inhibitor compared to either drug alone as an adjuvant therapy

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Introduction
There is always been a need for safe and effective adjuvant therapy in type 1 Diabetes not just for glycemic control but also for cardio-renal benefits.
Objectives
To evaluate whether addition of DPP-4 inhibitors reduces the ketogenic potential of SGLT2i when used as an adjuvant therapy in type 1 Diabetes.
Materials & Methods
20 type 1 Diabetes subjects above 18 years of age with poorly controlled glycemia (HbA1c 7 to 10%) were included in the study. At baseline along with physical examination, biochemical parameters-FPG, PPG, HBA1C, beta-hydroxybutyrate and fasting Glucagon were collected. This cohort was then treated with sitagliptin for 3 months, dapagliflozin for 3 months and combination of sitagliptin and dapagliflozin for 3 month adjuvant to insulin. At the end of each 3 months period anthropometric and biochemical parameters were assessed.
Results & observation
The plasma Glucagon levels compared with the baseline (30.99pg/ml), did not change with sitagliptin (29.89 pg/ml), increased significantly with dapagliflozin (55.89pg/ml) [+24.9pg/ml ($P < 0.05$)] and the combination treatment failed to reduce the Glucagon level 49.37pg/ml. The median ketone (beta-hydroxybutyrate) levels compared to the baseline [0.11(0.04 -0.87)] were numerically lower with sitagliptin [0.06(0.02 - 0.33)] and higher with dapagliflozin [0.14(0.04 - 1.16)]. However, the combination treatment failed to reduce the ketone levels [0.17(0.02 - 0.92)]. There was a statistically significant improvement in glycemic parameter, HbA1c with each of the intervention. On comparing with the baseline the mean difference of HbA1c after sitagliptin was 1.39%, after dapagliflozin was 1.08% and after the combination treatment was 1.59%. This was achieved with no change in the insulin dose. There was a reduction in weight, BMI, SBP and DBP with individual as well as combination treatment. Change in waist circumference was minimal.
Conclusions
Sitagliptin and dapagliflozin either alone or in combination as adjuvant therapy in type 1 diabetes results in a significant improvement in glycaemia. Sitagliptin failed to reduce fasting plasma glucagon and blood ketone (beta-hydroxybutyrate) levels when added to dapagliflozin. It thus appears that the ketogenic potential of dapagliflozin cannot be brought down by addition of sitagliptin. Thus, DPP4 inhibitors and SGLT2 inhibitors can be a useful adjuvant in the therapy of type 1 DM, but SGLT2 inhibitors should be used only after understanding the potential risk for ketosis.

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Development and Validation of Blood Glucose Measurement Knowledge Scale - BGM-Knowledge Scale

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Aim
Self-monitoring of blood glucose has an important place in ensuring diabetes management. This study aims to develop a reliable instrument to assess blood glucose measurement knowledge in diabetic patients. The purpose of the scale is to assess blood glucose measurement knowledge in diabetic patients.
Method
The data were collected from 240 patients in the diabetes polyclinic of a training and research hospital between March and September 2022. The scale item pool was created using the data obtained from the literature review and expert opinions. A validity analysis was performed for construct, content, and convergent validity. Kuder-Richardson-20 and test-retest reliability were used to assess the reliability of the scale.
Results
Among the patients included in the study, 57.9% were female, and 91.3% were married. The duration of diabetes was 10.78 ± 8.04 years; 79.6% had type 2 diabetes, and 37.1% used OAD + insulin. The researchers developed the final 3-point Likert-type "Blood Glucose Measurement Knowledge Scale (BGM-Knowledge Scale)" with 24 items. The scale content validity index was 0.91, and the convergent validity analysis result was 0.591 ($P < 0.01$). The scale items were subjected to one-factor CFA to confirm the structure of the scale with factorial weights ranging between 0.532 and 0.991. Kuder-Richardson-20 of the total scale was 0.90. The Kuder-Richardson 20 of the total scale was 0.90, and the test-retest result showed that the scale did not change over time (ICC = 0.947; $P < 0.01$).
Conclusion
The BGM-Knowledge Scale is a reliable and valid measurement tool to measure the knowledge level of diabetic patients about blood glucose measurement.
Keywords
Blood Glucose Measurement, Instrument Development, Scale, Validity, Nursing.
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Higher SHBG, Apo A1, HDL and adiponectin might be connected with lower cardiovascular risk in women with type 1 diabetes and LADA

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Aim
Low sex hormone-binding globulin (SHBG) is accompanied with onset of diabetes (DM) and increased cardiovascular risk (CVR). Proinflammatory cytokines, including adiponectin (APN) influence SHBG production. Lipid accumulation product (LAP) advocates as an indicator of increased CVR. We investigated the influence of different types of DM and sex on CVR through changes in SHBG and related risk factors.
Methods
Due to the non-normal distribution of individual dependent variables, they were log transformed [HbA1c, homocysteine (HCY), SHBG, interleukin-6 (IL-6), triglycerides (TG)]. Differences for analysed variables were tested using two factors analysis of variance (ANOVA) by gender, type of diabetes (DM1, DM2 and latent autoimmune: LADA) and their interaction. ANOVA and Tukey's post hoc test was also used for testing differences according to LAP quartiles (1st group: LAP < Q1; 2nd group: Q1 ≤ LAP < Med; 3rd group: Med ≤ LAP < Q3, 4th group: LAP ≥ Q3), separately in women and men. For all statistical tests, a significance level of 5% was considered statistically significant.
Results
SHBG level was significantly higher in women (especially in DM1) in comparison to men, and in autoimmune diabetes (DM1 and LADA) in comparison to DM2. There was no difference in SHBG between DM1 and LADA. Statistically significant interaction indicates that SHBG does not behave approximately equally between men and women according to the type of diabetes. APN level was significantly higher in women, without differences according to type of DM. High density lipoprotein (HDL) and apolipoprotein A1 (ApoA1) were higher in women and those with autoimmune diabetes (DM1 and LADA) in comparison with DM2, with no statistical difference between DM1 and LADA. Significant differences were determined in women and men for Apo A1, HDL, TG and HCY according to LAP quartiles. In women significant differences were determined for SHBG, fasting C-peptide (FCP) and IL-6; the difference for APN was bordered (P = 0.068). When the differences were significant, higher quartiles of LAP are characterised with increased TG, HCY, FCP and IL-6, whereas SHBG, ApoA1, APN and HDL were decreased.
Conclusions
Lower values of SHBG, HDL i Apo A1 in men and in DM2 pointed at higher CVR. APN was significantly higher in women without the difference according to the type of DM, while SHBG, HDL, and ApoA1 levels were higher in women and those with DM1 and LADA in comparison with DM2 suggesting CV protection in women with autoimmune diabetes.

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Machine learning-derived low density lipoprotein cholesterol (LDL-C) estimation agrees better with directly measured LDL-C than conventional equations in individuals with type 2 diabetes mellitus.

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Introduction
Elevated low-density lipoprotein cholesterol (LDL-C) is an important risk factor for atherosclerotic cardiovascular disease (ASCVD). Direct LDL-C measurement is not widely performed. LDL-C is typically estimated using the Friedewald (FLDL), Martin-Hopkins (MLDL) or Sampson (SLDL) equations, which may be inaccurate at high triglycerides (TG) or low LDL-C levels. We aimed to determine if machine learning (ML)-derived LDL-C levels agree better with direct LDL-C than conventional equations in patients with type 2 diabetes mellitus (T2DM).
Methods
We performed a retrospective cohort study on T2DM patients from a multi-institutional diabetes registry in Singapore from 2013 to 2020. Directly measured LDL-C values were compared against LDL-C values estimated by the FLDL, MLDL and SLDL equations, and ML models using linear regression (LR), random forest (RF) and k-nearest neighbours (KNN) using measures of agreement and correlation. Values were considered discordant if estimated LDL-C was <1.8 mmol/l but directly measured LDL-C was ≥1.8 mmol/l as this might lead to undertreatment in a real-world setting. A repeat train and test was performed on the subset of patients with TG values >4.5 mmol/l.
Results
11,475 patients with 39,417 sets of unique lipid panel results were included in the final analysis. 31,533 sets of results were used in the training set and 7,884 sets of results were used in the test set. All three ML models demonstrated better goodness-of-fit with lower root-mean-square-error values than any of the conventional equations, as well as stronger correlation with higher R^2 and r values. Of the three ML models, LR performed the least well (rmse 0.231, R^2 0.954 and r 0.977, P < 0.001) as compared to RF (rmse 0.209, R^2 0.962 and r 0.981, P < 0.001) or KNN (rmse 0.212, R^2 0.961 and r 0.98, P < 0.001). All three ML methods had much lower discordance rates (LR 2.17%, RF 2.18%, KNN 2.04%) than conventional equations (FLDL 23.14%, SLDL 17.90%, MLDL 14.22%). ML methods performed less well in the subset of patients with TG >4.5 mmol/l, although all three models still demonstrated better goodness-of-fit and correlation. Discordance rates were lower as well (LR 3.69%, RF 3.69%, KNN 2.30%), although the MLDL equation had the lowest discordance rate in this subgroup (1.84%).
Discussion
Conventional LDL-C estimation equations have disadvantages and are reported to perform poorly at high TG levels. ML methods may offer an alternative to allow more accurate estimation of LDL-C and to reduce misclassification and undertreatment in T2DM patients at high ASCVD risk.

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P96

Development and Validation of the Blood Glucose Measurement Competence Evaluation Form- BGM-CEF

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Aim
Self-monitoring of blood glucose has an important place in ensuring diabetes management. For diabetic individuals to measure their blood glucose level correctly with recommended frequency and technique, their blood glucose measurement technique, knowledge, and skills should be checked regularly with reliable measurement tools. This study aimed to develop a reliable instrument for assessing blood glucose self-monitoring skills in diabetic patients. The purpose of the scale is to evaluate the level of blood glucose self-monitoring in diabetic patients.
Method
This is a methodological study. The scale item pool was developed in line with the data obtained from the literature review and expert opinions. Validity analyses were evaluated with construct validity and content validity. Cronbach's alpha coefficient, test-retest and parallel form reliability were used to assess reliability. In determining the study sample, it was planned to have a ratio of 10 times the number of scale items and data collected from 207 patients. The study data were collected through face-to-face interviews held with the participants by the researchers in June-December 2021 in a diabetes clinic of a research hospital.
Results
Among the patients included in the study, 60.4% were female, diabetes duration was 10.42 ± 8.14 years, 78.3% had Type 2 diabetes, 35.7% used OAD + insulin, and 78.74% performed the recommended number of blood glucose measurements. In the study, a 3-point Likert-type "Blood Glucose Measurement Skill Assessment Form" consisting of 17 items was developed. The Scope Validity Index of the scale is 0.86. Seventeen items explained 79% of the total variance. One-factor Confirmatory Factor Analysis was performed to confirm the structure of the scale with factor weights ranging between 0.606 and 0.990. Cronbach's alpha of the total scale was 0.82. Intraclass Correlation Coefficient was 0.975 (P < 0.01), and the correlation coefficient of parallel form reliability was 0.611 (P < 0.01).
Conclusions
The blood Glucose Measurement Competence Evaluation Form-BGM-CEF is a valid and reliable measurement tool which assesses the blood glucose self-measurement skills of diabetic patients.
Keywords
Blood Glucose Measurement, Instrument Development, Scale, Validity, Nursing.
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Bruns-Garland syndrome (diabetic amyotrophy) associated with SGLT2 inhibitor and its rapid HbA1c improvement: a case-report

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Background
Bruns Garlands syndrome is a rare disorder in people living with diabetes, manifesting as unilateral or bilateral muscle pain, weakness and atrophy in the proximal region of the lower limbs. Herein, we present the case of a patient with Bruns-Garland syndrome caused by sodium/glucose co-transporter 2 inhibitors (SGLT2i).
Case description
A 55-year-old male with background of type 2 diabetes for 5 years, and currently on oral therapy, presented to the emergency admissions unit with ketosis, acidosis and borderline hyperglycaemia (ketones 6 mmol/l, pH 7.21 and blood glucose of 11 mmol/l, respectively). On further questioning, his diabetes control was suboptimal with some mild tingling sensation in his lower limbs first noticed a year ago; Empagliflozin was added to his therapy at that time, resulting in significant weight loss of about 8 kgs over 6 weeks and a substantial reduction in HbA1c from 103 to 48 mmol/mol in less than 6 months. On examination, he had widespread vitiligo, and proximal muscle wasting with bilateral lower limb weakness, reduced reflexes and paraesthesia, suggestive of peripheral neuropathy. Baseline myopathy screening was negative. Imaging studies were negative for sinister causes of weight loss. MRI spine was inconclusive, suggesting mild degenerative changes with multifocal disc prolapses and nerve root impingements, but no spinal canal stenosis. Nerve conduction studies of upper and lower limbs revealed a moderately severe, length dependent sensorimotor axonal neuropathy. This was confirmed with electromyography indicating an axonal peripheral neuropathy, with superimposed bilateral lumbar plexopathy/femoral neuropathy, suggestive of acute on ongoing neurogenic changes in bilateral lower limbs distally and proximally. Despite HbA1c improvement, his symptoms further progressed to debilitating proximal myopathy, with severe paraesthesia and burning sensation over his thighs in the next few months, despite Vitamin B12 levels replacement therapy.
Conclusion
Rapid improvement of HbA1c with SGLT2i or a direct effect of SGLT2i can significantly worsen background neuropathic changes leading to Bruns-Garland type diabetic amyotrophy. With the widespread use of SGLT2i, it is important that physicians treating patients with diabetes recognise these symptoms and consider this association in patients developing fatigue and weakness.

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P98

Investigation of Brain CD47 Expression and Its Relation with Cognitive Functions in Diabetic Mice Models

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Background
Diabetes Mellitus (DM) is an endocrine disorder resulting in hyperglycaemia that affects many vital organs of the body like the brain. The molecular mechanisms underlying dementia, memory loss and cognition dysfunction caused by DM are still not very clear. CD47 is a cell surface protein working in the homeostasis of the immune system. The causal relationship of CD47 has been shown in neurodegenerative diseases. CD47 also has a role in pancreatic islet cells and their maintenance in T1DM models.
Aim
Tha aims of the study are to determine cognitive funcitons in healthy and diabetic mice, to examine CD47 expression in brain tissue of healthy and diabetic mice and to determine its relationship with cognitive functions in T1DM and T2DM mice models.
Methods
This study was done using 39 CD1 male mice which were grouped as control ($n=12$), T1DM ($n=11$) and T2DM ($n=16$). T1DM and T2DM were induced by streptozocin and high-fat diet, respectively. Glucose levels of 200mg/dl or higher at the 2nd hour of oral glucose tolerance test established the diagnosis of DM in the T2DM group. Blood glucose of the mice was measured from the tail tip blood every week in all groups. Cognition tests {Control Open Field (COF) test, Y-Maze test, Novel Object Recognition (NOF) tests] were conducted to evaluate the animals' (control and type 1 DM group) cognitive functions. After sacrification, immunofluorescent staining and imaging were done to investigate the expression of CD47 in hippocampus region of brain tissue (in all 3 groups).
Results
The cognitive scores in the 2 out of 3 tests (COF, $P=0.03$; NOR, $P=0.01$,; Y-Maze, $P=$NS) in the T1DM group were significantly lower compared to the controls. CD47 expression was increased in both the T1DM and T2DM mice compared to controls ($P=0.014$). No correlation was observed between CD47 expression and cognitive functions in the T1DM mice.
Conclusion
Cognitive scores are decreased in T1DM mice compared to controls. CD47 expression is increased in the brains of diabetic mice compared to controls. There does not seem to be any correlation of CD47 expression and cognitive functions in diabetic mice. The explanation may be that CD47 levels in the brain may be elevated as a way of cells to protect themselves from excess blood glucose independent of cognitive functions.

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P99

Debilitating post-prandial hypoglycaemia as a sole presentation of coeliac disease responding to gluten free diet and plasma exchange for autoimmune neuromyotonia

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Post-prandial hypoglycaemia (PPH) can be associated with debilitating symptoms. Causes include altered physiology post-bariatric and upper gastrointestinal (GI) surgery and rarely noninsulinoma pancreatogenous hypoglycemia syndrome and insulin antibodies. We present a case of 49y female with no prior GI surgery presenting with debilitating hypoglycaemia with blood glucose falling to 2.8 mmol/l responding to glucose. Freestyle Libre monitoring confirmed hypoglycaemia 2-3 h post meals in keeping with PPH. BMI- 30.3, HbA1c-47 mmol/mol, am cortisol-462 nmol/l. The usual dietary recommendations were difficult to implement due to xerostomia in Sjogren's syndrome (SS) requiring mashed diet with fluids increasing diet's glycaemic index and GI transit. Patient also had autoimmune neuromyotonia presenting with muscular twitching and cramping responding well to regular plasma exchange (PLEX) sessions. Interestingly, patient observed improvement in intensity and frequency of her hypoglycaemia after PLEX raising a possibility of autoimmune cause. We postulated that PLEX might have either somehow improved her GI mobility by alleviating neuromyotonia or removed other untested antibodies involved in autoimmune hypoglycaemia (TTG IgA, insulin antibodies or insulin receptor antibodies). Although she did not have typical GI symptoms apart from mild bloating, TTG IgA were positive at 46.2 u/ml (0-15), endomysial antibodies negative. Duodenal biopsies showed increased intraepithelial lymphocytes, but no definite villous blunting confirming coeliac disease (CD). Gluten free diet (GFD) was commenced with a complete and sustained resolution of hypoglycaemia. Patient described GFD effect on her hypoglycaemic symptoms and quality of life as life changing.
Discussion
CD should be considered in work up of PPH especially in patients with other concurrent autoimmune diagnoses. CD can lead to reduced GI glucose absorption, but the exact mechanism of PPH in our case was intriguing. Concurrent mechanisms such as gut dysmotility in neuromyotonia, diet in Sjogren's syndrome and possibly presence of untested insulin antibodies might have compounded presentation in our case. Neuromyotonia presents with muscle cramps due to peripheral nerve hyperexcitability mainly affecting limbs and trunk. However, it has been reported that autonomic nervous system can also rarely be affected, which may present with gut dysmotility or excessive sweating. Testing for antibodies to insulin or insulin receptor was considered after hypoglycaemia response to plasmapheresis but was deferred given her complete response to GFD. Antibodies to insulin bind insulin after its postprandial secretion and subsequently release it independently of glycemia, predisposing to hypoglycaemia. Autoantibodies to the insulin receptor typically cause severe insulin resistance, but rarely they can also cause hypoglycaemia.

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P100

Gastrointestinal symptoms in patients with Diabetes Mellitus: Prevalence and associated factors

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Backgroud and Aim
Gastrointestinal (GI) symptoms are reportedly common in diabetes mellitus (DM) with a conflicting data on its prevalence in this specific population. The aim of our study is to determine the prevalence of GI symptoms and its associated factors.
Methods
This is a cross-sectional study conducted on 60 patients with DM. Anthropometric parameters, glycemic control, duration of diabetes and diabetic treatment were collected. Lower and upper GI symptoms were recognized using a questionnaire containing 10 questions about the frequency of GI symptoms that had been troublesome in the preceding 3 months. The frequency of each symptom was rated on a 4-point Likert scale and coded as not at all, rarely, sometimes or often. For the purposes of this analysis, a positive answer was recorded when the troublesome symptom was reported to occur sometimes and often.
Results
Mean age was 48,1 ± 15,46 years with female predominance (68.4%). More than two thirds (77.1%) of patients had type2DM treated by insulin in 79.4% of cases and 41.3% had hypertension treated with Renin-angiotensin-aldosterone system inhibitors, Calcium channel blockers, Betablocker and Thiazide diuretics in 83.3%,35.1%,29.4.% and 23.5% of cases respectively. In the whole population study, lower GI symptoms were noted in 54.2% of patients including abdominal pain, diarrhea, constipation, and flatulence, reported in 35.4%,0%,47.9%,47.9% of cases, respectively. Upper GI symptoms were noted in 33.3% of patients including vomiting, heartburn and gastroesophageal reflux symptoms, reported in 14.6%, 22.9% and 31.3% of cases respectively. Upper GI symptoms were significantly associated with type2 diabetes (29.7% vs 2.7%; $P=0.02$). Diabetes duration and treatment, glycemic control and hypertension treatment were not significantly associated with upper GI symptoms. Lower GI symptoms were significantly associated with type2 DM(51.4% vs 8.1%; $P=0.04$) and treatment with Calcium channel blockers (35.5% vs 0 %; $P=0.04$). Glycemic control and diabetes treatment and duration were not significantly associated with lower GI symptoms.
Conclusion
Type2 DM was associated with higher prevalence of upper and lower GI symptoms. No significant association was established with diabetes control, duration and treatment. However, our study highlights the effect of calcium channel blockers on GI symptoms, supported by other studies[1].
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P101

Role of C-peptide, body mass index and age in classification of diabetes

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Introduction
Classification of diabetes is challenging in some cases, especially in the presence of inaugural ketosis with a negative autoimmune laboratory test. The aim of our study is to determine the role of age, body mass index (BMI), and fasting plasma C-peptide (FCP) in the classification of diabetes.
Methods
This is a descriptive cross-sectional study that included 51 patients aged between 20 and 65 years hospitalized at the Endocrinology Department of the Military Hospital of Tunis for inaugural ketosis without a precipitating factor, with a duration of diabetes ranging from 6 months to 5 years. They underwent a metabolic biological assessment, an autoimmune laboratory test (anti-GAD65 + anti-IA2 antibodies), a fasting plasma C-peptide level. Our patients were divided into two groups: 31 patients with positive anti-GAD65 and/or anti-IA2 antibodies (AC+) and 20 patients with negative antibodies (AC-). Clinical and laboratory data were collected from medical records.
Results
Our population included 45 men and 6 women. Mean age was 34.3 ± 10.8 years. A family history of type 1 diabetes and type 2 diabetes were present in 11.8 % and 60.8 % of the cases respectively. Hypertension, dyslipidemia, obesity, and thyroid disease were reported at 9.8 %, 17.6 %, 21.6 %, and 9.8 % respectively. The mean age at onset of diabetes in AC+ patients was 27.5 ± 8.3 years and 36.3 ± 10.1 years in AC- patients ($P=0.002$). The mean BMI was 24.5 ± 3.4 Kg/m^2 in AC+ patients and 28.2 ± 6.7 Kg/m^2 in AC-patients ($P=0.024$). FCP level was 0.6 ± 0.7 ng/ml in AC+ patients and 1.7 ± 1 ng/ml in AC-patients ($P<10^{-3}$). An FCP level greater than 0.8 ng/ml was positively correlated with the absence of autoimmunity ($P<10^{-3}$). Its area under the ROC curve was 0.850. Its sensitivity was 84% and specificity 85%.
Conclusion
The classification of diabetes is based on several factors including the age of onset, body mass index (BMI) and FCP levels. These markers along with the autoimmune status can be used to differentiate between type 1 and type 2 diabetes, and to adjust the therapeutic regimen.

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P102

People With Newly Diagnosed T2DM Showed Significant Improvement in Glycemic Control and Effective Weight Management After Completion of Fitterfly Diabetes Digital Therapeutics Program

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Background and aim
Early glycemic control and weight reduction in diabetes has been associated with prevention of progression of β-cell dysfunction and reduction in diabetes-related complications. Digital therapeutics (DTx) platforms can provide evidence-based therapeutic interventions to improve glycemic control using sustainable behavior change. This study aims at assessing the real-world effectiveness of the Fitterfly Diabetes program in improving glycemic control and weight management among people with newly diagnosed T2DM.
Methods
De-identified data of 102 participants with T2DM (diabetes duration <1 year, mean age: 42.96 ± 11.54 years, gender: 30.39% (31/102) female) was analyzed. All the participants completed 90-days on the program and were provided with the Fitterfly mobile application for digital logging of meals and physical activity, remote lifestyle coaching, and live video consultations by experts (psychologists, physiotherapist and nutritionist). The participants were divided into 3 categories based on baseline BMI: normal (≤ 22.9 kg/m^2), overweight (23.0-24.9 kg/m^2), and obese (≥25.00 kg/m^2). The outcomes were evaluated at beginning and end of the program. All the data has been shown as median (IQR).
Results
Among all the participants, the baseline median HbA1c, weight, and BMI was found to be 7.00 (6.30, 8.52) %, 76.20 (70.00, 87.25) kg, and 27.70 (24.64, 30.90) kg/m^2 respectively. Reduction in HbA1c, weight, and BMI was observed by -0.75 (-2.30, -0.20) %, -3.00 (-5.00, -1.00) kg, and -1.00 (-1.88, -0.39) kg/m^2 respectively ($P<0.0001$ for all). Among participants with baseline HbA1c of ≤ 6.4 %, 6.5-8.4%, 8.5-10.5%, and ≥10.6% the reduction in HbA1c was observed by -0.20 (-0.30, 0.00) %, -0.70 (-1.40, -0.30) %, -2.95 (-3.45, -2.15) %, and -5.50 (-6.40, -3.85) % respectively ($P<0.01$ for all). After completion of program, 70.59 % (72/102) participants had achieved recommended HbA1c value ≤ 6.5 %. Reduction in BMI among participants in normal, overweight, and obese category was observed by -0.77 (-1.06, -0.10) kg/m^2, -0.69 (-1.34, 0.15) kg/m^2 and -1.20 (-1.96, -0.46) kg/m^2 ($P<0.01$ for all) respectively.
Conclusion
The Fitterfly Diabetes DTx program led to improved glycemic control and effective weight management among people with newly diagnosed T2DM. The program can help in providing continuous support for implementing lifestyle changes and can help in holistic management of diabetes.

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P103

Transition from childhood to adult care in type 1 diabetes mellitus: Single-center experience

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Introduction
Type 1 diabetes mellitus (T1DM) requires lifelong management, and a well-designed protocol may facilitate transition from child-centered healthcare systems to adult-oriented systems.
Aim
We aimed to evaluate sociodemographic data, clinical features and laboratory parameters that may affect the transition period and post-transition process in T1DM patients.
Materials and Methods
We retrospectively analyzed 64 patients with T1DM who were transitioned from pediatric to adult endocrinology outpatient clinic in Istanbul University, Istanbul Faculty of Medicine. Patients were followed up between 2001-2022 and completed their pediatric follow-up and participated in the pediatric-to-adult transition. The patients have been transferred to adult care with two different transition models. In model 1, transition was conducted in a single meeting, in model 2 it was conducted in a 4-6 month period. Demographic data, clinical and metabolic parameters, presence of diabetic complications and comorbidities, and treatment modalities were examined.
Results
Sixty-four patients were included in the analysis (43.7% female, age at diagnosis 9.4 ± 3.9). The mean age at last visit in pediatric care and at transition were 17.3 ± 0.5 and 20.2 ± 1.4 years, respectively. The median time in adult care follow up was 3.3 (min 0.3-20.9) years except for 5 subjects who lost-to-follow-up after one visit, and 4 subjects who were recently transferred. Mean body mass index at the time of transition was 24.1 ± 1.7 kg/m^2. While frequency of obesity was 1.6% in last pediatric visit, it increased up to 9.6% in last adult care visit. Use of insulin pump in adult care was higher (4.7% vs 12.5%; $P = 0.11$). Total insulin doses were significantly higher at transition than in last adult care visit (0.95 vs 0.75 IU/kg/day; $P < 0.01$). Basal insulin ratio was higher in adulthood (43.1% vs. 52.8%; $P < 0.01$). Routine control visit per year for diabetes care was higher in pediatrics follow-up ($P < 0.01$). Mean HbA1c was significantly lower in adulthood (8.9% vs. 8.3%; $P < 0.01$). Frequency of autoimmune thyroiditis and coeliac disease did not differ in pediatric and adult care. Although frequency of micro and macrovascular complications increased in adult care, no significant difference was found in acute and chronic complications. There was no difference between transition models 1 and 2 regarding diabetes care.
Conclusion
Obesity has increased in adulthood. Although total insulin doses decreased in adulthood, basal insulin ratio increased. Diabetes control get better in adulthood. Planned transition models have positive impact on diabetes care of adult patients.
Keywords
Type 1 diabetes mellitus, transition, diabetes care
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Effects of Diospyros Kaki Derived Exosomes on Beta Cell Homeostasis

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Introduction
Exosomes are nanoparticles containing bioactive molecules reflecting individual physiological status, regulating metabolism, and repairing damaged tissues. Exosomes are extracellular vesicles with nano-sized features (30-150 nm) involved in cell-to-cell communication and maintaining homeostasis. The function of exosomes is different according to their cargo and they can contain lipids, proteins and nucleic acids. Exosomes originating from mammalian cells as well as plant cell-derived play an important role in interspecies interaction. Exosomes, which are a very important discovery in studies aimed at elucidating the pathophysiology of diabetes, are still being investigated for their roles in treatment methods and cell interactions. In our study, we aimed to examine the effects of Diospyros Kaki-derived exosomes on beta cell homeostasis.
Methods
Three different doses of Diospyros Kaki-derived exosome were given to pancreatic beta cells isolated from spraque dowley rats in vitro. In order to evaluate the toxic effect of given date exosomes on beta cells, Mts analyzes were first measured at 24, 48 and 72 h. As it can be seen from MTS analysis, 50 mg/dl was found as optimum dose for treatment. After choosing the effective dose, total RNA isolation, cDNA and PCR analyzes were performed. As a result of PCR experiments, the amount of increase and decrease in gene expressions were analyzed.
Results
Effects of administration of Diospyros Kaki-derived exosomes on beta cells were analyzed via MTS and PCR techniques. After optimum dose were defined by MTS analysis, diabet specific genes such as preproinsülin, Transforming growth factor beta and Pdx-1 expressions were analyzedvia PCR. In addition, expression of preproinsülin, Transforming growth factor beta and Pdx-1 genes which are spesific for for the growth, secretion function, and survival of beta-cells, increased 3, 4 and 2 fold changes respectively. Furthermore, Diaspyros Kaki derived exosomes significantly increased beta-cell proliferation upon 50mg/ml concentration and no toxic effects were observed.
Conclusion
This study demonstrates the contribution of Diospyros Kaki-derived exosomes to beta cell proliferation in a pancreatic beta cells culture modelling diabetes mellitus. Our findings suggests that the use of Diospyros Kaki-derived exosomes should potentially be considered and studied in the future in the treatment of beta-cell associated diabetes mellitus.
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P105

New risk score for cardiovascular mortality in frail elderly people with type 2 diabetes

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Background
Cardiovascular mortality is the leading cause of death in elderly people with diabetes. Traditional cardiovascular risk factors are not principal predictors for cardiovascular events in frail elderly.
Aim
This prospective study examined biomarkers associated with cardiovascular mortality in 253 community dwelling elderly aged 65 to 99 years. Patients were divided into four main groups: GROUP A-Patients with type 2 diabetes and history of MACE; GROUP B-Patients with type 2 diabetes, without MACE; GROUP C-Patients without diabetes, with MACE; GROUP D-Patients without diabetes and without MACE– the control group.
Methods
Patients were followed for a six months period. We checked medical records for presence of new MACE or cardiovascular death. MACE was defined as self-reported and medically documented myocardial infarction and/or stroke. Cardiovascular mortality was defined as mortality from myocardial infarction, heart failure, stroke, aneurism, or complications after vascular surgery. Baseline biochemical measurements were made from fasting blood samples performed at home on the morning of the baseline examination. We investigated traditional risk factors, inflammatory markers and albumin as marker of malnutrition. We also considered other standard biochemical measurements as potential risk factor. The associations between mortality risk and different biomarkers were assessed using Cox proportional hazards (PH) regression. We used cutoff points based on ROC analysis to form dichotomy variables from significant multivariable predictors. Differences in Kaplan-Meier survival curves were tested by Log rank test.
Results
Significant multivariate predictors for cardiovascular mortality were: albumin $<$ 40 g/l, BMI <25 kg/m^2, total bilirubin <10.5µmol/l, BUN ≥ 6.5 mmol/l and hsCR$P \geq 2.25$ mg/l. We built the score system with these five predictors. The score was positive if someone had three or more of these five predictors positive and we called it inflammatory-malnutrition-renal involved score (IMRIS). Presence of prior MACE raised risk for cardiovascular mortality approximately twice (RR 2.113; $P < 0.001$), and positive IMRIS nearly four times (RR 3.908; $P < 0.001$). In group with T2D relative risk for cardiovascular mortality with positive IMRIS was 3.884 ($P < 0.001$), vs.3.871 ($P < 0.001$) in group without T2D. In group with prior MACE relative risk for cardiovascular mortality with positive IMRIS was 4.326 ($P < 0.001$), vs.3.185 ($P = 0.001$) in patients without MACE. In the control group low HDL-cholesterol was the only predictor for cardiovascular mortality (HDL$\leq$ 1.51, RR 2.643; $P = 0.004$).

Conclusion
In our study new proposed IMRIS score was predictive for cardiovascular mortality in patients with T2D regardless of traditional cardiovascular risk factors and metabolic control.

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P325

Insulin resistance and hyperglycemia induce mitochondrial dysfunction and a metabolic towards use of gluconeogenic amino acids in epithelial kidney cells

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Diabetic nephropathy (DN) and insulin resistance (IR) in kidney cells are considered the main cause of end-stage renal failure. Additionally, hyperglycemia and increased fatty (FA) acids are observed in patients with type 2 diabetes mellitus, where lipid accumulation has been correlated to IR. Nonetheless, the impact of IR in early disease stages is still unclear. Moreover, proximal renal tubular cells have high mitochondrial content where aerobic respiration is their primary mechanism of ATP production, being particularly susceptible to metabolic and mitochondrial injury from hyperglycemia. Herein, we will explore the impact of mild (11 mM) to severe hyperglycemia (22 mM) as well as IR under normoglycemia (5 mM) in *in vitro* conditions in renal epithelial cells' metabolic and mitochondrial bioenergetics profiles. To do so, we used a human epithelial kidney cell line (HK-2), which was cultured in increasing concentrations of glucose (5mM, 11 mM and 22 mM). Lipid cytotoxicity was used to induce insulin resistance (IR), through the administration of Palmitic Acid (PA), for 24 h. The effect of hyperglycemia and IR in the consumption/production of metabolites were analyzed by nuclear magnetic resonance. Additionally, *in vivo* mitochondria function was assessed by seahorse analytics, as well as mitochondrial complex I (CI) and II activities. We also evaluated free FA oxidation and lipid accumulation. Our results demonstrated that PA was able to induce IR and altered the metabolic fingerprint in HK-2 secretome since Glucose, Glutamine, Lactate, Pyruvate, Alanine, Isoleucine, and Glutamate concentrations increased in comparison to the same conditions without PA-induced IR, where gluconeogenic amino acids played a key role to supply energy. It was also observed that FA was not the preferential carbon source for HK-2 cells, resulting in its accumulation. Mitochondrial parameters (basal respiration, ATP production, proton leak, maximal and spare respiration capacity) of HK-2 cells are increased in mild hyperglycemia conditions but decreased when cultured in high hyperglycemia with IR. Furthermore, in this condition, there was a decrease in the CI activity of the electron transport chain. Our data demonstrated that progression from mild to severe hyperglycemia induces a metabolic shift, where gluconeogenic amino acids are crucial to supply energy requirements. Furthermore, this progression allied to IR induced mitochondrial dysfunction, suggesting that this time point between mild to severe hyperglycemia might disclose a "window" of opportunity to help to target and treat the early kidney disease associated with hyperglycemia and IR.

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P326

Effects of a combinatory treatment with semaglutide and a NPY Y2 receptor selective PYY 3-36 analogue in diet-induced obese rats: surpassing bariatric surgery?

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Background
Combinatory treatments with analogues of incretins might mimic the beneficial effects of bariatric surgery. We could show in the past that a combinatory treatment with PYY 3-36 and liraglutide leads to a similar body weight loss as Roux-en-Y gastric bypass (RYGB). We hypothesize that a combination of semaglutide and a modified PYY 3-36 analogue with increased selectivity for the neuropeptide Y receptor type 2 (NNC0165-1273) exceeds the weight-reducing effects of bariatric surgery.
Methods
High-fat (45%) and high-fructose diet (HFD)-induced (8 weeks) obese male Wistar rats were randomized into the following treatment groups: (1) NNC0165-1273 + semaglutide, (2) semaglutide, (3) saline. NNC0165-1273 was given continuously via osmotic minipump (0.08 µmol/kg/d), semaglutide was given once daily s.c. at a dose of 120µg/kg. Animals were kept on a free choice high- and low-fat diet after start of the respective intervention. Body weight and food preference were measured daily for 8 weeks post intervention.
Results
NNC0165-1273 + semaglutide treatment led to an impressive and long-lasting body weight loss (max. -23.9%), which was superior to semaglutide monotherapy (max. -9.9%) and saline treatment (+8%). Compared to an earlier study with diet-induced obese rats, NNC0165-1273 + semaglutide was even more effective than RYGB. Additionally, NNC0165-1273 + semaglutide led to a strong decrease of HFD preference.
Conclusions
A combination of NNC0165-1273 and semaglutide is highly effective in terms of body weight loss in diet-induced obese rats and might be superior to the weight reducing effects of RYGB.

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The impact of Diabetes Mellitus in patients with Pulmonary Fibrotic Disease; disease progression and bronchoalveolar lavage evaluation

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Rationale/Objective
Diabetes Mellitus (DM) and Interstitial lung Disease (ILD) share common pathogenetic pathways involving inflammatory cells and in particular monocytes and macrophages. Diabetic patients are at higher risk of developing pulmonary fibrosis, whereas DM is a major comorbidity in ILD patients. In our study, we analyzed retrospectively patients with ILD and aimed to examine differential characteristics between patients with and without DM, including disease parameters and alveolar macrophage evaluation.
Material and methods
256 patients with Pulmonary Fibrosis (Idiopathic or not) seen in the Department of Respiratory Medicine and in Endocrinology and Diabetes Clinic the University Hospital of Heraklion from January 2014 to July 2022, were enrolled; 76 with DM and 180 without DM. Clinical characteristics of all patients including age, smoking habits, BMI, pulmonary function at baseline and disease progression up to 2 years follow-up, were collected. In all of the included patients, bronchoscopy was performed and bronchoalveolar lavage (BAL) was obtained. The levels of mtROS were measured in fresh BAL alveolar macrophages by flow cytometry using MitoSOXRed (Invitrogen) superoxide indicator.
Results
Our results showed that ILD patients with DM had a statistically increased smoking history, and a tendency to rapid disease progression, although not significant. In accordance with previous reports, we did not find any other significant difference between disease baseline characteristics or disease progression and mortality between ILD patients with or without DM. Interestingly, we observed a significantly increased macrophage population in BAL of patients with DM. In the subgroup analysis of IPF patients, there was a trend of increased percentage of alveolar macrophages in BAL of patients with DM, while there were decreased levels of oxidized mitochondria in macrophages of these patients.
Conclusions
Our preliminary results showed increased macrophage population in BAL of ILD patients with DM, while there were reduced levels of oxidized mitochondria in the alveolar macrophages of IPF patients with DM. It is unknown if targeted anti-

diabetic treatment results in these observations, and further studies are required to assess whether antidiabetic medications could decrease mitochondrial ROS in alveolar macrophages of ILD patients.

Keywords
Pulmonary fibrosis, interstitial lung disease, alveolar macrophages, diabetes mellitus

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How do diabetes-related ketoacidosis outcomes compare between hospitals? Results from a quality improvement project

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Background
The appropriate and timely management of diabetes-related ketoacidosis (DKA) has important implications for patient outcomes. Despite the availability of national management guidelines to promote standardised care, we do not know if there are differences in DKA outcomes and complications between hospitals.
Aim
To assess for differences in DKA outcomes and treatment complications between hospitals.
Methods
This retrospective study was done as part of an ongoing quality improvement project which utilises a centralised DKA registry. All episodes satisfying national diagnostic criteria admitted to six hospitals (anonymised as A to F) in the West Midlands region of the United Kingdom from October 2021 to September 2022 were included. People aged <16 years or who self-discharged before biochemical resolution of DKA were excluded. We collected pseudonymised data on dates and times of hospital admission, discharge, DKA diagnosis, and DKA resolution, alongside the number of hyperkalaemic, hypokalaemic and hypoglycaemic events during DKA treatment. We used the Independent-Samples Kruskal-Wallis test to look for differences in DKA duration and length of stay between hospitals. Chi-square analysis was performed to assess for differences in the proportion of DKA episodes complicated by hyperkalaemia, hypokalaemia and hypoglycaemia between sites.
Results
In total, 442 DKA episodes were analysed. We found significant differences between hospitals in length of patient stay (median in days; A-2.1, B-2.5, C-3.5, D-3.6, E-2.5, F-3.0; $P<0.001$), DKA duration (median in h; A-13.3, B-13.4, C-18.5, D-15.1, E-17.1, F-16.3; $P=0.002$), and the proportion of DKA episodes complicated by hypokalaemia (A-37.3%, B-19.6%, C-39.3%, D-25.4%, E-45.2%, F-43.6%; $P=0.01$). However, there were no significant inter-hospital differences in the proportion of DKA episodes complicated by hyperkalaemia (A-33.3%, B-26.1%, C-28.7%, D-30.3%, E-16.7%, F-33.3%; $P=0.534$) or hypoglycaemia (A-15.7%, B-15.2%, C-17.2%, D-9.2%, E-23.8%, F-17.9%; $P=0.197$).
Conclusions
Despite use of similar guidelines, there are significant variations in some DKA outcomes and treatment complications between hospital sites. Ongoing use of a centralised data collection system with periodic analysis may help to identify best practices to be shared between centres. Going forwards, this may facilitate more uniform patient care and hence minimise inter-hospital variations in DKA outcomes.

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RNA-seq profiling from white adipocyte to brown adipocyte-like cells trans-differentiation of 3T3-L1 by β3-adrenergic stimulation

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Beige adipocytes can be induced from white adipocytes (WAT) and precursors upon stimulation by cold temperatures and act like brown adipocytes (BAT) to increase energy expenditure. Most *in vivo* studies examining the mechanisms for the induction of beige/brown adipocytes have focused on subcutaneous white adipose tissue (sWAT) in the mouse. To better understand the development of beige/brown adipocytes from mammalian sWAT, we induced WAT and BAT from 3T3-L1 preadipocytes by exposure to classical differentiation protocols. We transdifferentiated BAT from 3T3-L1 white adipocytes by stimulus β3-adrenergic agonist (CL316,243). Furthermore, we used RNA-Seq to investigate whether differentiation protocol can influence the transcriptome of adipocyte browning. The expression of white and brown fat-specific markers was increased in WAT and BAT after 10 days of differentiation. At 6 days differentiation treatment of white adipocyte with CL316,243 for 48 h produced more adipocytes with multilocular phenotype, typical of brown adipocytes. An increase in uncoupler protein-1(UCP1) and Peroxisome proliferator-activated receptor-γ co-activator-1α (PGC-1α) and decrease aP2, white adipocyte marker suggested that CL316,243 transdifferentiates browning. RNA-seq was used to determine genes regulated by the fat browning process and identify the key differences between the two functionally distinct adipocytes. Taken together, we provide detailed adipocyte-specific gene expression profiles affected by adipocyte trans-differentiation.

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Cabergoline counteracts adipose and skeletal muscle lipid accumulation through promoting oxidative pathway: an *in vivo* and *in vitro* preclinical study

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Obesity, characterized by an abnormal body fat accumulation mainly caused by a chronic imbalance between energy intake and expenditure, is a massive public health problem. Targeting excessive fat deposition in adipose tissue and ectopic fat accumulation in skeletal muscle through promoting lipid oxidation pathway may represent a promising strategy to counteract obesity. This study aims at investigating the effects of cabergoline (CAB), a dopamine agonist, on adipose and skeletal muscle tissues' lipid accumulation by monitoring the protein levels of the main lipogenic markers in adipose tissue and by analyzing lipid oxidation pathway in both adipose and skeletal muscle tissues in *in vivo* and *in vitro* preclinical models. To this aim, 2 groups of 60-days aged male Wistar rats receiving a high-fat and fructose-rich diet for 28 days were analyzed: one receiving an oral dose of CAB 0.6 mg/kg of body weight every 3 days for a total duration of 2 weeks (HFFC), the other one receiving placebo (HFF). Moreover, in white adipocytes 3T3L1, lipid accumulation through Red Oil staining and oxidative pathway through WB analysis were performed after 3 days of CAB 10^{-10}-10^{-6} M. HFFC visceral adipose tissues showed a significant decrease of PPARγ ($P<0.05$) and adiponectin ($P<0.01$) proteins, with a concomitant strong inhibition of leptin (60%) and FAS (75%) proteins compared to HFF. Moreover, HFFC visceral adipose tissues showed a significant reduction of pACC ($P<0.05$) and a strong increase in pAMPK Thr172 (74%) with a concomitant moderate stimulation of PKA catalytic subunit (PKA-Cα) (18%). Similarly, HFFC subcutaneous adipose tissues showed a significant decrease of leptin ($P<0.01$) and adiponectin ($P<0.01$) and a strong inhibition of PPARγ (70%) compared to HFF. Moreover, HFFC subcutaneous adipose tissues displayed a strong increase in pACC Ser72 (30%) associated with a significant stimulation of PKA-Cα ($P<0.001$) compared to HFF. Likewise, HFFC soleus tissues showed a significant increase in pACC Ser72 ($P<0.05$) associated with a significant stimulation of PKA-Cα ($P<0.01$) compared to HFF. Concomitantly, in white 3T3L1, Red Oil demonstrated that CAB 10^{-8}M and 10^{-6}M significantly inhibited lipid accumulation ($P<0.001$), while WB revealed that CAB 10^{-6}M significantly stimulated pAMPK Thr172 ($P<0.05$) and slightly decreased PPARγ, leptin and FAS proteins compared to untreated 3T3L1. These preliminary preclinical data demonstrate a novel CAB lipolitic effect in murine adipose and muscle tissues mediated by oxidation pathway.

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Exploration of Clinical Improvements Following Setmelanotide in Patients With Bardet-Biedl Syndrome

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Background
In patients with Bardet-Biedl syndrome (BBS), signaling impairments in the melanocortin-4 receptor (MC4R) pathway lead to hyperphagia and severe obesity, which negatively impact quality of life (QOL). We evaluated the impact of setmelanotide, an MC4R agonist, on age-appropriate weight-related parameters, hunger, and QOL in a Phase 3 trial of patients with BBS to further characterize clinical benefit in this patient population.
Methods
Patients $\geq$6 years old with BBS and obesity were enrolled into a Phase 3 trial (NCT03746522) and received 52 weeks of setmelanotide treatment. Hunger was assessed with an 11-point Likert scale in patients $\geq$12 years old without cognitive impairment. QOL was assessed in adults using the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) and in pediatric patients using the Pediatric Quality of Life Inventory (PedsQL). Clinically meaningful improvements in weight-related parameters were defined as $\geq$5% reduction in body weight for adults and $\geq$0.2-point decrease in BMI Z score and/or $\geq$5–percentage point decrease in percent of the 95th BMI percentile for pediatric patients. Clinically meaningful improvement in hunger was defined as a $\geq$1-point within-patient reduction in hunger score. In adult and pediatric patients, patient-relevant improvements in QOL were defined as an increase in IWQOL-Lite score of 7.7-12 and increase in PedsQL score of $>$4.4, respectively. Stabilization of weight-related parameters was also assessed.
Results
In total, 28 of 32 patients (88%) had clinically meaningful or patient-relevant improvements that met thresholds in $\geq$1 measure at the last study visit. Three of 4 patients without improvement showed weight stabilization; thus, 31 of 32 patients (97%) experienced clinically meaningful and/or patient-relevant improvement or weight stabilization. Setmelanotide was generally well tolerated; 1 patient discontinued study drug during placebo treatment because of an adverse event.
Conclusions
Most patients with BBS showed clinically meaningful or patient-relevant improvement following setmelanotide, as measured by decreases in age-appropriate weight-related parameters, decreases in hunger, and overall improvements in QOL. Clinical benefit from antiobesity medications should be assessed beyond weight loss, especially in patients with BBS.

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Enhanced antibacterial activity of green ZnO NPs against multi-drug resistant bacterial pathogens from diabetic foot ulcer using Aristolochia indica

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Introduction
Diabetic foot ulcers (DFU) have developed into a more common complication among people with uncontrolled diabetes, who also have higher morbidity rates and are more prone to polymicrobial infections that spread quickly and cause irreparable tissue damage. The most difficult aspect of treating diabetic foot ulcers (DFU) is the rising prevalence of multi-drug resistant germs, which necessitates the use of a novel antimicrobial agent.
Objective
In this study, the bactericidal effects of ZnO nanoparticles (ZnO NPs) green produced from *Aristolochia indica* against Multi-drug Resistant Organisms (MDROs) were examined.
Method
Transmission electron microscopy (TEM), Atomic Force Microscopy (AFM), and zeta potential measurements were used to characterise ZnO nanoparticles. To ascertain if the effects were bactericidal or bacteriostatic, MIC/MBC assays were carried out. At 1x MIC and 2x MIC doses of ZnO NPs, time-kill tests, protein leakage, and flow cytometric analyses assessed bacterial cell death. The results of each experiment were run in triplicate, and they were presented as the mean SEM of three separate experiments. $P<0.04$ was regarded as statistically significant. The means were statistically compared using One-way ANOVA, followed by post hoc Dunnett's and Tukey's Multiple Comparison Tests using GraphPad Prism version 5.
Results
ZnO NPs with a zeta potential of -21.8 $\pm$ 2 mV and a size of 22.4 nm showed exceptional bactericidal activity, with MIC/MBC ranging from 24 to 300 g/ml and a considerable decline in viable count after 1 hour. Bacterial cell death caused by ZnO NPs was confirmed by protein leakage and flow cytometric analysis.
Conclusion
Due to its improved bactericidal effects even against clinical bacterial infections that are practically resistant to existing stronger antibiotics, the current work offers new insight into the development of green produced ZnO NPs as an alternative therapeutic agent. However, more research is required to fully understand the mechanism underlying antibacterial activity. It is also recommended that this synthesis method can be used to other biological applications, such as larvicidal and antifungal medicines. This study came to the conclusion that the green synthesis technique offers a trustworthy, environmentally friendly method for creating antimicrobial ZnO NPs to fight antibiotic medication resistance.

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Diabetes Distress among Type 1 Diabetic adolescents in India

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Introduction
Diabetes distress, a term used to describe negative emotions associated with diabetes, is the key factor responsible for the elevated risk of psychological burden and compromised self-management. The aim of this study is to determine the prevalence of diabetes-related distress among adolescent patients with type 1 diabetes (T1D) and to ascertain various factors associated with it.
Materials and methods
In this cross-sectional study, 102 T1D patients with age 12-20 years visiting a diabetic clinic in the Department of Diabetology from March 2022 to October 2022 were enrolled. The patient's demographic and clinical details were noted in a pre-designed proforma. T1D distress scale (T1DDS) was used to measure diabetes distress and distress was classified as severe, moderate, and no/little distress.
Results
Of the 102 T1D patients, 36 % ($n=36$) had diabetes-related distress, of which 31% had moderate and 3 % had severe distress. The average total distress score was 1.70 $\pm$ 0.62 and higher mean scores were of powerlessness, negative social perception, and eating distress. Distress was higher among females, in those with the onset of diabetes in teens rather than in childhood. There is a significant impact of glycated haemoglobin (HbA1c) on the severity of diabetes distress as demonstrated by Pearson's correlation ($r=.530$, $n=102$, $P=<.001$)
Conclusion
The present study highlights the association of diabetes distress in adolescents with various factors, most significantly poor glycemic control, and therefore emphasizes the need for developing psychological interventional strategies in

routine diabetes care to improve the mental well-being and self-management of diabetic patients.

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Usefulness of Intermittent Intersticial Glucose Monitoring in Patients Admitted to The Intensive Care Unit of The Hospital Universitario San Cecilio in Granada

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Objective
The carbohydrate metabolism dysfunctions are common in critical ill patients with diabetes or stress hyperglycaemia and the correct management of them has an important prognostic value. Despite its limitations, capillary glucose (CG) was collected more than arterial glucose (gold standard) because of its good correlation. However, the usefulness of intermittent intersticial glucose monitoring (IGM) in keeping blood glucose within target range in critical ill patients its controversial. Therefore, we will evaluate IGM and CG correlation in critical ill patients with diabetes or stress hyperglycaemia.
Materials and Methods
Prospective longitudinal observational study with 6 diabetic or stress hyperglycaemia patients admitted to the Intensive Care Unit (ICU). Demographic (sex, age), clinical (DM, hypertension, obesity), hemodynamic (need for vasoactives) and metabolic (A1c-type glycosylated hemoglobin (HbA1c) determined by laboratory analysis, presence of angiopathic complications, CG and IGM measurements (in mg/dl)) variables were collected. The statistical analysis was performed with the IBM SPSS v.25 programme (Statistical significance $P<0.05$).
Results
67% were males with a mean age of 65.5 ± 21.5 years. 100% were hypertensive and 50% obese. 67% were type 2 diabetic with a mean HbA1c 6.5 ± 1.6% and 75% had angiopathic complications. 67% required vasoactives. Statistical analysis shows a strong and positive correlation between CG and MIG values ($r=0.8$, $P=0.0$).
Conclusions
There is a strong and positive correlation between MIG and CG values, which highlights the probable usefulness of the first one in patients admitted to the ICU. Therefore, it could be feasible as a glycemic management tool in the critically ill patient by improving GC measurements limitations. More studies are needed for prove this.

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Dapagliflozin Improves Glycemic control and Liver Function with Body Weight Loss as Add-on therapy to Metformin Plus Evogliptin: A 24-week, Randomized, Double-blind, Clinical Trial

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Background and aims
The efficacy and safety of dapagliflozin as add-on therapy in patients with type 2 diabetes mellitus (T2DM) and inadequate glycemic control with evogliptin and metformin combinations was investigated.
Materials and methods
Patients with HbA1c of 7.0% to 10.5% receiving evogliptin 5mg and metformin ≥1000 mg were randomized to receive dapagliflozin 10 mg/day ($n=99$) or placebo ($n=99$) for 24 weeks. The primary endpoint was change from baseline in HbA1c at week 24. Prespecified subgroup analyses of the change in HbA1c were performed in patients with screening HbA1c values <8%, ≥8%. Secondary endpoints were changes from baseline in 2hr-postprandial plasma glucose, body weight, uric acid, liver function and lipid parameters.
Results
HbA1c (baseline mean±SD: dapagliflozin 7.87±0.72%; placebo 7.77±0.68%) decreased significantly from baseline with dapagliflozin (placebo-subtracted least square [LS] mean change±SE: –0.70±0.11%, $P<0.0001$). In patients with higher screening HbA1c values (≥8%), placebo-subtracted LS mean decreases in HbA1c seen with dapagliflozin were numerically greater (–0.79±0.20% compared with –0.65±0.12% in patients with lower HbA1c values (<8%)). LS mean difference in 2hr-postprandial plasma glucose after breakfast at week 24 with dapagliflozin vs placebo was -27.48±7.63 mg/dl($P=0.0004$). Significant reductions in uric acid and body weight were observed with dapagliflozin relative to placebo at week 24 [(LS mean difference± SE: -0.38±0.11 mg/dl ($P=0.0007$), -1.79±0.29 kg ($P<0.0001$), respectively). Compared to placebo, dapagliflozin treatment significantly reduced ALT, r-GT and hepatic steatosis index (HIS) at week 24 (placebo-subtracted LS mean change –2.77±1.37 U/l, $P=0.0444$; -9.46±3.56 U/l, $P=0.0085$; -0.91±0.33, $P=0.0062$). Patients receiving dapagliflozin showed placebo-subtracted LS mean increases in total and HDL cholesterol (6.73±2.82 mg/dl, $P=0.0179$; 2.78±0.87 mg/dl, $P=0.0016$, respectively). Adverse events occurred in 27.55% of patients receiving dapagliflozin and 27.27% receiving placebo. Adverse events were similar across treatment groups with a low overall risk of hypoglycemia (~3%).
Conclusions
Dapagliflozin improves hyperglycemia and fatty liver and well tolerated over 24 weeks as add-on to patients with type 2 diabetes inadequately controlled by metformin plus evogliptin combination.

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P336

Oral Semaglutide Improves Metabolic Outcomes in Type 2 Diabetes: A Spain-based Study

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Objectives
To evaluate the changes in HbA1c, basal glucose, weight, and lipid profile in patients with type 2 diabetes after starting oral semaglutide.
Methods
This study was conducted in Madrid, Fundación Jiménez Díaz, Infanta Elena and General de Villalba hospitals. A total of 75 patients with type 2 diabetes were

	Comparison		
	Basal	**6 months**	**Differences**
Basal glucose (mg/dl) $^{\alpha}$	165,0±5,9	135,0±5,0	-30,0 ($_{95\%}$IC: -41,1 a -19,0) **
HbA1c (%) $^{\alpha}$	7,85± 0,16	6,67±0,14	-1.18 ($_{95\%}$IC: -1,50 a -0.85)**
Weight (kg) $^{\alpha}$	95.1±1,5	89,8±1,4	-5,4 ($_{95\%}$IC: -6.4 a – 4,3) **
BMI (kg/m^2) $^{\alpha}$	34.5±0,5	32.6±0,5	-1.9 ($_{95\%}$IC: -2.3 a – 1,6) **
Total Cholesterol (mg/dl) $^{\alpha}$	171,7±5,5	153,7±4,3	-18,0 ($_{95\%}$IC: -27,8 a – 8,2)**
LDL-cholesterol (mg/dl) $^{\alpha}$	90,8±4,2	79,0±3,8	-11,8 ($_{95\%}$IC: -18,5 a – 5,1)**
Triglycerides (mg/dl) $^{\beta}$	159($P_{25\text{-}75}$:121-208)	131($P_{25\text{-}75}$:102-172)	-24($_{95\%}$IC: -38 a -4)**
HbA1c <7% $^{\Phi}$	33,3%	67,1%	+34,2% ($_{95\%}$IC: 22,6 a 48,6)**
	HbA1c reductions by basal HbA1c $^{\alpha}$		
HbA1c > 7%		-1,3 ($_{95\%}$IC: -1,7 a -0,8)**	
.HbA1c > 8%		-1,6 ($_{95\%}$IC: -2,0 a -1,2)**	
HbA1c > 9%		-1,8 ($_{95\%}$IC: -2,3 a -1,3)**	

** $P<0.01$; * $P<0.05$

included. The mean age was 62.0 ± 10.5 years and 60% were men. The mean duration of diabetes was 7.3 ± 6.6 years, and 66.7% had hypertension, 67.6% had dyslipidemia, 14.9% were smokers, 23.0% had sleep apnea, and 26.4% had microvascular disease. Basal treatment included insulin in 12.0%, metformin in 86.7%, SGLT2i in 48%, DPP4i in 41.9%, GLP1-Ra in 1.3%, repaglinide in 8.1%, and Sulphonylurea in 2.7%. A total of 58.3% of patients reached a dose of 7 mg, and 41.7% reached 14 mg. 4 patients discontinued the treatment, 2 due to adverse effects and 2 due to administrative problems. Gastrointestinal adverse effects were reported in 16% of patients. The study had a follow-up period of 7.3 ± 6.6 months. Paired T-Student test for parametric data (α), Wilcoxon test for non-parametric data (β), and McNemar test for proportions (ϕ) were used for statistical analysis.
Results
The following changes were observed after starting oral semaglutide:
Conclusions
Oral semaglutide was associated with significant improvements in HbA1c, fasting glucose, weight, and lipid profile in patients with type 2 diabetes. The treatment was well tolerated, with a low incidence of adverse effects. The results of this study support the use of oral semaglutide.

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P337

PDE4 Inhibitors Act in The Brain to Ameliorate Metabolic Parameters in Diet-Induced Obesity

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Obesity is associated with peripheral and central low grade inflammation characterized by the increase in pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF). Phosphodiesterase 4 (PDE4) modulates the inflammatory responses and its inhibitor can strongly reduce TNF release and inflammation. Additionally, PDE4 knockout mice were shown to be resistant to diet-induced obesity (DIO). The aim of this study was to investigate the role of central and peripheral effects of PDE4 in DIO. To attain this purpose, mice treated were treated with rolipram, a PDE4 inhibitor capable of crossing the blood brain barrier, or YM-976, a brain-impermeable inhibitor. All experimental protocols were approved by the Ethics Committee for Animal Use of the Ribeirao Preto Medical School. Male C57Bl6 mice were fed with either chow or high-fat diet (HFD; 60% fat) for 10 weeks and in the 8th week they received daily subcutaneous injections vehicle (VEH), rolipram (2mg/kg) or YM-976 (2mg/kg). During the experimental period, food intake and body weight were monitored and at the end of the study inguinal, retroperitoneal and brown fat pads were collected for analysis. Rolipram decreased the absolute value and change in body weight in the HFD group, which was associated with a decrease in epididymal and retroperitoneal fat pad weight, with no effect in the chow group. Remarkably, rolipram was able to decrease energy intake and energy efficiency, as well as increase energy expenditure in the HFD-treated animals. Consistent with these results, histological analysis showed that rolipram decreased the adipocyte size of inguinal adipose tissue and reduced the whitening of brown adipose tissue in the HFD group. In contrast to rolipram, YM-976 inhibitor was unable to ameliorate the metabolic changes in DIO. These results indicated that mechanisms in the brain are required to the beneficial metabolic effects of PDE4 inhibitors on DIO and reinforce PDE4 as a potential target for the treatment of obesity.

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P338

High-fat diet causes transgenerational alteration in the expression of Obesity-related genes in mouse seminal vesicles

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Obesity incidence is increasing globally at an alarming rate, particularly amongst children and young adults. Male obesity has been linked with a reduction in sperm quality and consequently decreased fertilization rates. Seminal vesicles are considered fundamental for male fertility and though for men's health. Vesicle seminal secretion contributes to a significant volume of seminal fluid, being extremely important for semen coagulation and sperm motility. Recent studies suggest that an obesity-inducing lifestyle combined with genetic changes can cause epigenetic mutations. Obesity-related genes (ORG) have been pointed out as causes for an overweight, suggesting that children born from obese parents could have a genetic predisposition to develop metabolic disorders. This project aimed to unveil molecular mechanisms related with the inheritance of an overweight through seminal vesicles. We hypothesized that ORG, Fat mass and obesity (FTO), Melanocortin-4 receptor (MC4R), Glucosamine-6-phosphate deaminase 2 (GNPDA2), and Transmembrane protein 18 (TMEM18) were present and could have a role in seminal vesicles and consequently in production of seminal fluid over three generations. Samples of seminal vesicle tissue were selected from mice included in the following experimental design: the first generation (F0) was divided into 3 groups ($n = 6$ per group) according to administered diet. Mice are randomly fed after weaning with standard chow (CTRL); HFD for 200 days or transient HFD(HFDt) (60 days of HFD + 140 days of standard chow). Subsequent generations (F1 and F2; 6 mice per generation) are fed with chow diet. Mice are euthanized 200 days post-weaning. RNA was extracted from the seminal vesicles of the 54 animals and used to evaluate the mRNA abundance of MC4R, FTO, GNPDA2 and TMEM18 through quantitative Polymerase Chain Reaction (qPCR) in the 3 groups of the 3 generations of mice. Early results suggest a significative abundance increase in all ORG genes analysed in generation F1 for all diet groups. We observed a tendency to increase the abundance of ORG from the F0 generation to the F1 generation and a further decrease in the F2 generation. Our results suggest that a high-fat diet is capable of causing changes in the expression of ORGs in the seminal vesicles of offspring of parents with poor eating habits. That is, HFD is capable of causing transgenerational damage that may manifest itself in children and grandchildren who may be more predisposed to obesity and possible fertility problems.

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P339

Therapy of overweight and obesity resistant to behavioral treatment in the adult population with metabolic comorbidities. A network meta-analysis

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Background
Overweight and obesity are an increasing concern for public health worldwide. Obesity is a chronic, progressive and relapsing disease associated with the development of several comorbidities which may improve after weight loss. The first step in the management of weight excess includes life-style modifications but, in the long-term, obesity is frequently resistant to life-style changes only. Surgical procedures and medical treatments have, therefore, been developed for improving the outcomes of this chronic disease.
Aim
Of the study was to identify the best treatment for weight loss, and their timely use, as add-on to lifestyle intervention for adults with resistant overweight and obesity complicated by metabolic comorbidities: pre-diabetes, type 2 diabetes mellitus, hypertension, hyperlipidemia, and non-alcoholic fatty liver disease.
Methods
This systematic review and network meta-analysis (NMA) included searches of Medline/PubMed, Embase and Cochrane Library from inception to May 16, 2022, for randomized controlled trials (RCTs) of weight-lowering drugs that are available in Italy (Naltrexone/Bupropione-N/B, Orlistat, Liraglutide 3 mg/daily, Semaglutide 2.4 mg/weekly) and of bariatric surgery procedures (Sleeve gastrectomy, Roux en Y Gastric Bypass (RYGBP), Gastric Banding, and other

modalities of Gastric Bypass). Target population were adults with overweight or obesity (BMI 27-40 kg/m2) and at least one of the above reported comorbidities. The study was registered with PROSPERO (CRD42022351409). From the retrieved 2928 studies, this NMA included 45 RCTs on pharmacological and 20 RCTs on surgical treatments. Weight loss. As compared with lifestyle intervention, the add-on effect of the different evaluated interventions was (mean, CI 95%):

- Orlistat, -2.93 kg (4.34 lower to 1.52 lower) (mixed evidence, certainty of the evidence moderate)
- Liraglutide, -3.85 kg (6.19 lower to 1.52 lower) (direct evidence, certainty of the evidence high)
- Semaglutide, -9.83 kg (14.12 lower to 5.5 lower) (direct evidence, certainty of the evidence high)
- N/B, -4.5 kg (8.17 lower to 0.84 lower) (mixed evidence, certainty of the evidence moderate)
- Gastric banding, -12.26 kg (15.55 lower to 8.96 lower) (mixed evidence, certainty of the evidence moderate)
- Sleeve gastrectomy, -18.05 kg (21.66 lower to 14.44 lower) (mixed evidence, certainty of the evidence moderate)
- RYGBP, -24.71 kg (27.96 lower to 21.46 lower) (mixed evidence, certainty of the evidence moderate)
- Other gastric bypass, -21.74 kg (26.96 lower to 16.52 lower) (indirect evidence, certainty of the evidence moderate).

Conclusion

This NMA quantifies the effect of drugs and surgical treatments on weight loss that improved outcomes compared to lifestyle changes only. Surgeries were more effective than pharmacological treatments.

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P340

The Effect of Foot Care Protocol Applied to Individuals with Type 2 Diabetes on Foot Health Problems and Foot Care Behaviors

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Aim

The research was conducted as a randomized controlled experimental study to determine the foot health status of individuals with type 2 diabetes and the factors affecting them, to use a protocol to protect and improve foot health for individuals with diabetes, and to determine the effects of this protocol on foot health problems (regarding dermatology, orthopedics, circulation, sensory, footwear and self-care skills), foot health knowledge and foot care behaviors.

Materials and Methods

The population of the study consisted of patients with type 2 diabetes who applied to Hatay Training and Research Hospital Endocrinology, Metabolism and Diabetes Polyclinic. A total of 70 individuals with diabetes who met the research criteria were randomized to intervention and control groups at the start of the study. Data were collected using Diabetes Information Form, Foot Examination Form, Foot Care Knowledge Level Form, Nottingham Assessment of Functional Footcare (NAFF) and Foot Care Protocol Satisfaction Level Form. Four interviews were conducted with the intervention group while two were conducted with the control group. In the power analysis performed at the end of the study, the results of the comparisons were computed at 95%, 99% confidence interval, and $P<0.05$, $P<0.01$ significance level.

Results

As a result of the intervention in the study, a statistically significant difference was found between the groups regarding dermatological problems related to the feet, burning sensation in the feet, footwear and problems related to self-care ($P<0.01$). In addition, a statistically significant difference was found in the pretest-posttest scores of the intervention group regarding foot care knowledge level and Nottingham Assessment of Functional Footcare scores ($P<0.01$).

Conclusion

As a result, it was determined that the foot care protocol applied to individuals with type 2 diabetes increased the level of foot care knowledge and consequently reduced foot health problems.

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P341

Prevalence and Impact of Diabetes Mellitus in Adult Tuberculosis Patients;A Cross-Sectional Study

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Background

Both diabetes mellitus (DM) and tuberculosis (TB) are major public health problems and among the leading causes of morbidity and mortality worldwide. The TB-DM coexistence is known to complicate TB care, control and prevention. Globally, 10.4 million TB cases exists, of them 10 % are linked to DM. People with DM are at four to five times higher risk of getting infected with tuberculosis and evidence show poor TB treatment outcomes. This study purposed to evaluate the impact of diabetes mellitus on treatment outcomes in patients with active tuberculosis.

Materials and methods

A cross-sectional study was conducted in a tertiary health care center in Tirana, Albania. We analyzed the medical records of 140 patients hospitalized during in 2018–2019 with a diagnosis of pulmonary tuberculosis. Study subjects were adult tuberculosis patients hospitalized in our hospital and undergoing antituberculosis treatment. Data from study subjects were obtained by interview method using semistructured questionnaire consisting of socio-demographic and clinical parameters. To determine DM risk factors, one variable and multivariable logistic regression analysis was done with 95% confidence interval and P-value <0.05 considered significant.

Results

Out of 140 patients, the prevalence of DM was found to be 9.3 % ($n=13$) with average glucose values X = 145 mg/dl (min 120 — max 175 mg/dl), SD = 30. No significant differences were found between sex, residence, type and site of TB. Increasing age ($P<0.02$), male sex ($P=0.04$), and clinical manifestations like type of TB ($P=0.82$), multilobe involvement ($P=0.243$), other lung diseases ($P=0.154$) are not significantly associated with DM-TB comorbidity.

Conclusion

The prevalence of DM among TB patients in this study is high. The expanding burden of diabetes is increasing the risk of contracting tuberculosis and has a strong impact on TB treatment outcomes. The results of our study show that patients with TB-DM were at higher risk of treatment failure and mortality compared to those with TB without diabetes. Bidirectional screening for TB and DM along with planning and implementation of preventive and curative strategies will help early detection and prevent complications of comorbidity.

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P342

Characteristics of components of metabolic syndrome in patients with diabetic kidney disease depending on the phenotype of latent autoimmune diabetes in adults

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Background

Metabolic syndrome is a cluster of conditions (abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance with or without glucose intolerance) that occur together, increasing risk of cardiovascular diseases.

The objective

Of the study was to determine components of metabolic syndrome in patients with diabetic kidney disease (DKD) depending on the phenotype of LADA.

Methods

42 patients with LADA (19 patients with LADA1, 23 with LADA2) and DKD were examined, as well as 25 representatives of the control group. We studied blood pressure indicators, lipid profile, HOMA-IR index and anthropometric indicators: body mass index (BMI), waist circumference (WC) and waist circumference to hip circumference ratio (WC/HC).

Results

Arterial hypertension was found in 73,7% of patients with LADA1 and 78,3% of patients with LADA2 phenotype. HOMA-IR index was higher than normal in 26,3% of LADA1 patients and 91,3% of LADA2; it was increased in patients with LADA2 phenotype by 66.8% compared to control ($P<0.001$) and 2.8 times compared to LADA1 ($P<0.01$). Hypertriglyceridemia was registered in 31.6% patients with LADA1 and 56.5% of LADA2 patients; the indicator was higher by 84% ($P<0,05$) and 48.1% ($P<0,01$) compared to control group level respectively. High-density cholesterol level was abnormal in 26.3% of LADA1 patients and 43.5% of LADA2 patients; it was lower by 19.8% ($P<0.05$) and 43.9% ($P<0.001$) respectively compared to control. Abdominal obesity was registered in 47,8% of patients with LADA2; 42,1% patients with LADA1 and 39,1% with LADA2 have metabolically

unhealthy overweight phenotype. BMI in LADA2 group was 24.4% higher than the control indicator and 22.4% higher than the value in LADA1 group ($P<0.001$). WC was higher by 14.1% comparing LADA1/control ($P<0.05$), by 34.6% comparing LADA2/control ($P<0.001$) and by 18% in LADA2/lADA1 ($P<0.01$). The WC/HC ratio was the highest in the LADA2 group: by 31.3% compared to the control ($P<0.001$) and by 23.9% compared to the LADA1 group ($P<0.01$). In patients with LADA1 moderate positive relationships were found between fasting plasma glucose levels and BMI ($r=0.514$; $P<0.05$), HOMA-IR index and albumin-creatinine ratio ($r=0.479$; $P<0.05$); in LADA2 phenotype – between fasting plasma glucose and systolic blood pressure ($r=0.432$; $P<0.05$); negative correlations of medium strength – between glomerular filtration rate by the formula MDRD and BMI ($r=-0.485$; $P<0.05$) and WC/HC ($r=-0.483$; $P<0.05$).

Conclusion

The degree of insulin resistance, arterial hypertension, dyslipidemia and abdominal obesity as main components of metabolic syndrome significantly increase in patients with LADA2 phenotype which indicates the higher cardiovascular risk in this category of patients.

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P343

Prevalence of mutations in cublin-megalin receptor genes in Diabetis Mellitus: Subset analysis of an Indian NGS (Next Generation Sequencing) study

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Background

Diabetes mellitus (DM) is the commonest endocrinopathy, Worldwide. Amongst the protean complex genetic variations, cubulin gene and megalin gene mutations in diabetes are important in dictating genotype-phenotypic correlations and natural clinical course of diabetes. The genetic studies in this area are especially very sparse from Indian sub-continent. In this context, we analyzed the prevalence of cubulin (CBN) and megalin (LRP2) gene mutations, as part of NGS (Next-generations sequencing) in diabetes patient's visavis controls.

Methods

This is inter-disciplinary case control study conducted by collaboration between biochemistry department of a teaching medical institute, a tertiary care endocrinology hospital, and genetics lab. Institutional ethical committee approval was obtained. In this prospective study, CUBN gene polymorphisms and megalin (LRP2) gene polymorphisms in subjects with type 2 diabetes mellitus using real-time PCR and ThyroSeq v2 on the Ion Torrent PGM sequencer was employed. Mutations were also manually checked using the Integrated Genomics Viewer v2.4.10 to filter out false positives.

Results

The percentages of AA, AG and GG in cases were 12.5, 62.5 and 25 while in controls it was 70, 20 and 10 respectively. The allele frequencies of A and G alleles in patients are 0.44 and 0.56, while in controls were 0.80 and 0.20 correspondingly. The percentages of CC, CT and TT in cases were 47.5, 50 and 2.5 while in controls it was 60, 30 and 10 respectively. The allele frequencies of A and G alleles in patients are 0.73 and 0.27 while in controls were 0.75 and 0.25 correspondingly. The difference was statistically significant (P -value <0.05) for CUBN gene and non-significant for LRP2 gene.

Conclusions

The rs622342 polymorphism of SLC22A1 appears to be the commonest mutation in South Indian T2DM patients. Cubulin gene mutation was significantly and megalin gene was insignificantly associated with DM. However, it needs validation in larger cohort studies through assessing the additional variants of SLC22A1 gene at the mRNA levels. NGS helps in patient management, providing risk stratification and sub-classification of DM.

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P344

Changes in Glycemic Risk Index (GRI) and its Association with other Continuous Glucose Monitoring (CGM) Metrics after Automated Insulin Delivery System Initiation in Adults with Type 1 Diabetes

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Objective

To evaluate the GRI and its association with other CGM metrics after initiation of automated insulin delivery (AID) system in adults with type 1 diabetes (awT1D).

Methods

Up to 90 days of CGM data before and after initiation of an AID system from 185 awT1D were collected. GRI with hypoglycemia and hyperglycemia components and other CGM metrics were calculated using cgmanalysis R software and analyzed for 24-hour, nighttime, and daytime. GRI values were assigned to 5 GRI zones as zone A (0-20), zone B (21-40), zone C (41-60), zone D (61-80), zone E (81-100).

Results

After AID initiation, GRI, its two components and other CGM metrics improved significantly (Table-1). The percentage of people in each zone changed as follows: A: 10.8% to 24.7%; B: 23.8% to 58.4%; C: 36.2% to 15.1%, D: 20.5% to 0.5%, and E: 8.7% to 0%. GRI was correlated with time between 181-250 mg/dl before ($r=0.691$, $P<0.001$) and after ($r=0.818$, $P<0.001$) and time above 250 mg/dl before ($r=0.925$, $P<0.001$) and after ($r=0.920$, $P<0.001$). GRI was not correlated with time between 54-70 mg/dl before ($r=-0.029$, $P=0.698$) and after ($r=0.038$, $P=0.611$), and with time below 54 mg/dl before ($r=0.123$, $P=0.096$) and after ($r=0.140$, $P=0.058$). Improvement in nighttime, compared to daytime, was superior; as seen in increased TIR and decreased GRI ($P<0.001$ for both). GRI improved by 19.7 percentiles and TIR improved by 14.6 percent.

Conclusion

GRI was highly correlated with various CGM metrics above (but not below) target range, both before and after AID initiation. Improvement in GRI was greater than improvement in TIR, and both were significant, GRI, compared to TIR, was a better indicator for improved glycemia after AID initiation.

Table 1 Comparison of CGM metrics before and after AID initiation, n=185

	Before AID Initiation	After AID Initiation	P value
CGM wear time,%	81.25±16.9	88.44±12.71	<0.001
CGM data, days	76.39±18.8	81.11±16.47	0.002
Mean sensor glucose, mg/dl	167.57±29.23	150.32±18.36	<0.001
Glucose management indicator(GMI),%	7.3±0.7	6.90±0.44	<0.001
SD	59.40±13.17	49.16±10.12	<0.001
CV,%	35±5	33±4	<0.001
Time below range, <70 mg/dl(TBR),%	3.23±3.33	1.97±1.98	<0.001
Time between 54-70 mg/dl(TBR2),%	0.65±1.03	0.36±0.5	<0.001
Time below 54 mg/dl(TBR1),%	2.58±2.39	1.62±1.52	<0.001
Time in range, 70-180 mg/dl(TIR),%	58.95±17.29	73.56±11.66	<0.001
Time above range, >180 mg/dl(TAR),%	37.81±18.29	24.47±12.18	<0.001
Time between 181-250 mg/dl,(TAR1),%	24.99±8.92	18.87±7.75	<0.001
Time above 250 mg/dl(TAR2),%	12.83±11.26	5.60±5.15	<0.001
GRI	48.66±21.81	29.01±13.01	<0.001
GRI-Hypoglycemia component	2.72±2.85	1.65±1.68	<0.001
GRI-Hyperglycemia component	25.32±14.52	15.03±8.52	<0.001

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Vitamin D deficiency and gestational diabetes

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Introduction

Vitamin D deficiency is known to cause adverse outcomes in pregnancy and has shown to have an association with Gestational Diabetes Mellitus (GDM)

Aim

To evaluate the relationship between GDM and Vitamin D

Materials and Methods

In a retrospective study we explored the Vitamin D levels (Sufficient >50nmol/l - G1, Insufficient 25-50nmol/l - G2, Deficient <25nmol/l - G3), GTT results, diabetes status and pregnancy outcomes of 250 pregnant women of multiple ethnicities who attended the antenatal clinic between 2018 and 2022. Blood tests and glucose tolerance tests (GTT) were performed at 26-28 weeks of pregnancy. All patients were on Pregnacare (multivitamin tablets including Vitamin D 400IU from booking).

Results

Mean Vitamin D in G1 was 64.13 ±10.27 nmol/l, in G2 was 38.39 ± 7.26 nmol/l and in G3 was 20.15 ± 3.37 nmol/l. The mean fasting sugar in G1 was

5.00 ± 0.70 nmol/l, G2 was 5.13 ± 0.82 mmol and G3 was 5.73±1.24 mmol; $P=0.003$ for G3 vs G2 +G1, $P=0.005$ for G3 vs G2. Caucasian group had a mean Vitamin D of 45.15 ±16.75 nmol/l and in South Asian (SA) group 41.17± 18.03 nmol/l. GTT in the two groups were: 0 min –5.05 ± 0.82 mmol and 5.28 ± 0.92 mmol ($P=0.05$), and GTT 2 h –7.03 ± 2.20 mmol and 8.11 ± 2.17 mmol ($P=0.0007$) respectively. Mean BMI in Caucasian and SA group was 31.24 ± 7.25 and 28.64 ± 5.08 ($P=0.01$) and baby birth weight was 3.30 ± 0.48 kg and 3.05 ± 0.60 kg ($P=0.004$), respectively.

Conclusion

Pregnant women with low Vitamin D were found to have elevated fasting sugars irrespective of the ethnicity and South Asians are more prone to have GDM. Caucasians had higher BMI and larger babies.

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Sex-driven factors associated with anxiety and depression in Type 1 Diabetes Mellitus (T1DM) and Latent Autoimmune Diabetes in Adults (LADA)

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Aim

To analyze the prevalence of anxiety and depression in a large cohort of adults affected by autoimmune diabetes and to identify the associated factors, stratifying them according to sex.

Methods

We administered to 553 patients with autoimmune diabetes the questionnaires: Hospital Anxiety and Depression Scale (HADS), Diabetes Distress Scale, Diabetes-related Quality of Life and Diabetes Treatment Satisfaction Questionnaire. We excluded 119 patients with missing HbA1c ±4 months from HADS administration or incorrect HADS compilation (final cohort, $n=434$).

Results

Anxiety was reported in 132/434 subjects (30.4%), depression in 47/434 (10.8%). The group with anxiety had a larger proportion of females, higher HbA1c (median 56 mmol/mol [IQR 49-63] *vs* 59 [IQR 52-66]; $P=0.006$), higher average HbA1c in the previous 36 months (56 mmol/mol [IQR 50-63] *vs* 59 [IQR 54-66]; $P=0.002$), more individuals with HbA1c >48 mmol/mol (76.8% *vs* 90.2%; $P=0.001$), more CGM users (61.3% *vs* 71.2%; $P=0.046$) and lower Time in Range (60.1% *vs* 54.8%; $P=0.043$). The group with depression showed higher median age (47 years [IQR 33-59] *vs* 53 [IQR 42-59]; $P=0.015$) and superior prevalence of cardiovascular diseases (3.1% *vs* 12.8%; $P=0.002$) and retinopathy (31% *vs* 46.8%; $P=0.029$). There was greater emotional distress, and lower quality of life and treatment satisfaction (P equal or inferior to 0.005, for all), irrespective of sex. In females, CGM use was and independent risk factor for anxiety and older age for depression; in males elevated levels of Hb1Ac (a worse glycemic control) were an independent risk factor for both anxiety and depression. No differences in CGM-derived metrics were observed stratifying results by sex.

Conclusion

Nearly 1/3 of the patients with autoimmune diabetes suffers from anxiety and nearly 1/10 from depression. These conditions are associated with independent modifiable and non-modifiable characteristics, which are different between females and males.

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Abstract withdrawn

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Bexagliflozin in Patients with Type 2 Diabetes: Scoping Review of the Published Randomised Control Trials

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Introduction

US Food and Drug Administration (FDA) has recently approved bexagliflozin, a new SGLT2 inhibitor. We examined the outcomes and metabolic effects of Bexagliflozin across the published Randomised Controlled Trials (RCCTs)

Methods

A comprehensive literature search was done to extract publications from Medline-PubMed and Cochrane library, since inception till January 20, 2023, then screened and reviewed by two independent reviewers. Data including, study title, year of publication, name of the journal, study design, and the evaluated outcomes were charted for evidence synthesis. Scoping review was performed according to PRISMA-SR checklist. We included only the RCCTs for evaluation.

Results

We analysed 12 publications, and evaluated five RCCTs, with 1704 T2DM cumulatively contributing to the evidence base for Bexagliflozin. The mean duration of the trials (weeks) was 50(±42, minimum 12, maximum 96, 95% CI -1.6 to 102). The mean number of T2DM evaluated across RCCTs were 341(±62, minimum 288, maximum 426, 95% CI 264 to 418). Each of the RCCT has been distinct from each other for comparison with glimepiride, dose finding study, evaluation as monotherapy, comparison with sitagliptin and evaluation in patients with CKD stage 3a or 3b. The findings include, that bexagliflozin was noninferior to glimepiride in lowering HbA1c, was superior to glimepiride for decreases in body mass and SBP, and was associated with significantly fewer hypoglycaemic events than glimepiride; bexagliflozin confers substantial and dose-dependent benefits, is non-inferior to sitagliptin and provides benefits over sitagliptin in FPG and body mass. The results support the usage in patients with CKD stage 3a/3b CKD. The initial results of the Bexagliflozin Efficacy and Safety Trial (BEST) support the benefits in patients with high cardiovascular risk

Conclusions

The synthesis of the evidence from our analysis reflects that bexagliflozin has durable, clinically meaningful improvement in glycaemic control.

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Non Interventional Weight Changes are Associated with Alterations in Lipid Profile and in Trigycerides to Hdl-Cholesterol Ratio

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Background and aims

Obesity is associated with dyslipidemia through insulin resistance and adipokines secretion, and weight loss can improve obese patients' lipid profile. Here we aimed to assess whether non interventional weight changes are associated with alterations in the lipid profile, particularly the triglycerides (TG) to high density lipoprotein (HDL) cholesterol ratio (TG/HDL) which is an emerging marker for insulin resistance, the metabolic syndrome and an elevated risk for coronary artery disease.

Methods

This is a retrospective analysis of subjects referred to annual medical screening. BMI, low density lipoprotein (LDL)- cholesterol, TG and HDL levels were measured annually. Patients were divided according to the change in BMI between visits: reduction of > 5% ("large reduction"), reduction of 2.5-5% ("moderate reduction"), reduction of <2.5% or elevation of <2.5% ("unchanged"), elevation of 2.5-5% ("moderate increase") and elevation of >

5% ("large increase"). The primary outcomes were the change in LDL, TG, HDL and TG/HDLbetween visits.
Results
The final analysis included 18,828 subjects. Mean changes in LDL (mg/dl), TG (mg/dl), HDL (mg/dl) and TG/HDL (%) were associated with BMI changes and were -3.89, -11.00, +5.76, -13.20 for "large reduction" BMI group, -0.96, -0.91, +2.99, -1.71 for "moderate reduction" BMI group, +1.30, +5.36, +1.93, +5.26 for "unchanged" BMI group, +2.91, +12.50, +1.30, +13.00 for "moderate increase" BMI group, and +3.91, +17.70, +0.43, +19.70 for "large increase" BMI group, respectively ($P > .01$). The proportion of patients with > 10% rise in TG/HDL progressively increased with the relative change in BMI (20.6%, 30.2%, 37.5%, 46.2%, and 50.2% for "large reduction", "moderate reduction", "unchanged", "moderate increase", and "large increase" groups, respectively, $P > .01$). Compared to the "unchanged" group, the odds ratio for TG/HDL rise of > 10% was 0.43, 0.72, 1.43 and 1.68 for "large reduction", "moderate reduction", "moderate increase", and "large increase" groups, respectively ($P > .01$). Subgroups analysis by gender, initial TG/HDL and initial BMI revealed that the trends of TG/HDL change by BMI did not change significantly, albeit the association of TG/HDL by BMI was mildly mitigated in females.
Conclusions
Non-interventional weight changes, even modest, are associated with alterations in lipid profile.

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Loss of visceral adipose tissue may lead to a shortened aortomesenteric distance in congenital generalized lipodystrophy

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Introduction
Superior mesenteric artery (SMA) syndrome is a rare cause of abdominal pain due to proximal intestinal obstruction which is characterized by compression of the third portion of the duodenum secondary to the narrowing of the space between the superior mesenteric artery and aorta. The development of the SMA syndrome is primarily attributed to the loss of the intervening mesenteric fat. Lipodystrophy is a rare clinical syndrome characterized by the loss of adipose tissue that can affect the amount of visceral and mesenteric fat.
Method
We measured aortomesenteric distance (AOM) in patients with various forms of lipodystrophy. Sixty patients with lipodystrophy (11 males; 49 females; mean age 38 ± 13 years; 20 congenital generalized lipodystrophy, 30 familial partial lipodystrophy, and 10 acquired partial lipodystrophy) were included. An age-, gender- and BMI-matched control group (1:2) was generated from a cohort of subjects with hormone inactive adrenal incidentalomas. The AOM distance was measured on MR images.
Results
Median AOM distance was 10.8 mm (25-75 percentiles: 7.1-16.1 mm) in patients with lipodystrophy and 11.0 mm (25-75 percentiles: 8.0-15.5 mm) in the control group ($P=0.311$). Patients with congenital generalized lipodystrophy had lower AOM distance (8.2 mm [25-75 percentiles: 6.0-12.4 mm]; $P=0.024$) compared to controls and patients with familial partial lipodystrophy (vs. 12.4 mm [25-75 percentiles: 7.2-18.0 mm]; $P=0.059$). Twelve of 20 patients (60%) with congenital generalized lipodystrophy had an AOM distance of less than 10 mm, a risk factor that may predispose patients to develop SMA syndrome. Body mass index was positively correlated with AOM distance, both in the overall sample ($r=0.397$, $P<0.001$) and in patients with lipodystrophy ($r=0.485$, $P<0.001$). BMI was found to be a significant predictor of AOM distance in multivariate linear regression analysis including age, sex, and BMI ($r^2= 0.27$, $P<0.001$).
Conclusion
Visceral fat loss in lipodystrophy syndromes may pose a risk to SMA syndrome that is likely to only affect patients with generalized lipodystrophy. Abdominal pain is a common symptom in lipodystrophy mostly attributed to episodes of acute pancreatitis secondary to severely elevated triglycerides. SMA syndrome should be kept in mind in patients with generalized lipodystrophy who presented with abdominal pain, nausea, and vomiting, especially when the initial workup does not support a diagnosis of acute pancreatitis.

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High-fat diet promotes 3'mt-tiRNA-Met epididymosome enrichment which correlates to lower spermatozoa mitochondrial translation

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Metabolic and endocrine dysregulation induced by high-fat diet (HFD) can lead to decreased male fertility potential and have a negative impact on the offspring's metabolic health. Small non-coding RNAs (sncRNAs) were proposed as being potential mediators of metabolic queues across transgenerational inheritance. During development and epidydimal transit, spermatozoa become enriched with tRNA-derived stress-induced RNAs (tiRNAs). This sncRNAs class appears to be particularly important for sperm quality and embryo development, through processes that are now starting to be unveiled. Herein, we hypothesized that mitochondrial tiRNAs (mt-tiRNAs) are integrated into the spermatozoa through epididymosomes. Further, we propose that HFD can alter the mt-tiRNAs carried by epididymosomes, which can then impact sperm quality. To test our hypothesis, 4-week-old male C57BL mice were fed *ad libitum* with an HFD or standard diet (control) for 14 weeks. Size characterization showed no significant difference between epididymosomes vesicle size from the two groups, although the HFD group presented a tendency for a greater epididymosome concentration (nearly 2-fold). We also found an increased abundance of 3'mt-tiRNA^{Met} in epididymosomes from the HFD group. Under stressful conditions, tiRNAs expression often becomes upregulated at different somatic cell lines. Additionally, higher tiRNAs expression is usually correlated to decreased translation. To explore spermatozoa mitochondrial translation function, we assessed mitochondrial 12S rRNA abundance. HFD mice presented lower 12S rRNA levels on spermatozoa, as well as higher 3'mt-tiRNA^{Met} levels on epididymosomes when compared to the control group. A positive correlation between spermatozoa 12S rRNA expression levels and normal sperm morphology was also found. Concurrently, higher 12S rRNA expression levels were negatively correlated with spermatozoa tail defects. Our results suggest that mt-tiRNAs have an important role in spermatozoa HFD-induced stress (dys)regulation. Most particularly 3'mt-tiRNA^{Met}, expressed by the epididymis, carried by epididymosomes, and integrated into the spermatozoa, might take part in the molecular mechanisms by which the HFD induces deleterious effects on sperm quality with a potential negative impact on male fertility.

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Obesity in pediatric patients with Bardet - Biedl Syndrome – diagnostic hint and therapeutic challenge

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Introduction
Bardet-Biedl Syndrome (BBS) is an autosomal recessive disease and one of the most common causes of syndromic obesity. An excessive weight usually appears at an early age and affects almost 90% of patients. Mutations in BBS genes have been found to disrupt the function of the cilia, leading to disturbances of transduction satiety and hunger signals in hypothalamus and increased adipogenesis in the fat tissue.

Methods
We present a case series of eight pediatric patients (P1 to P8) with BBS (six boys and two girls) observed in one Medical Centre including two pairs of siblings.
Results
The age range at the moment of diagnosis was 1 month to 4 years (average 20 months). At presentation obesity was present only in four patients, whereas polydactyly and urinary system disorders was observed in six patients, psychomotor development delay in two patients. In two patients with kidney disorders and polydactyly, the genetic tests were ordered at the age of 2 and 6 months due to having ab older sibling with the diagnosis of BBS. Their weight-for-length z-scores at the age of one year were above 3.0 (P3 = 3.1, P5 = 3.7). The mutations in the following genes were confirmed: BBS10 (1), MKKS (P2, P3 – sibling, the same mutations), BBS7/BBS10 (P4, P5 - sibling, the same mutations), BBS7 (P6, P7, different mutations), BBS9 (P8). The duration of the follow up varied between 6 months to 9 years. All patients' parents received diet training and lifestyle intervention at every office visit. During follow up seven out of eight patients developed obesity at some point. Only P7 had never developed excessive weight (the highest BMI z-score 0.55). In six patients an excessive increase of body weight was observed, only in one case BMI z-score decreased (P8) and in another one remained stable during observation (P7). In P1 the obesity class 3 (BMI z-score 4.37) was diagnosed with multiple metabolic disorders (MAFLD, hypertension, insulin resistance, dyslipidemia). In the other one patient hypertriglyceridemia with increased LDL-cholesterol was found and in another three – isolated hypertriglyceridemia was present.
Conclusion
Obesity is one of the main therapeutic challenges while handling patients with BBS, even though it is not often the reason for starting diagnostics for this disease. It is necessary to bring awareness about this syndrome among pediatricians in order to allow for earlier diagnosis and ensure patients' better prognosis.

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Real-life outcomes of semaglutide therapy for weight loss

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Background
Obesity, a chronic relapsing disease, has become a global public health challenge**.** Semaglutide, a weekly glucagon-like peptide-1 (GLP-1) agonist which has shown unprecedentedly high efficacy in randomised controlled trials, was recently approved in Europe for weight loss. There is paucity of real-life data about its effectiveness and safety for weight management.
Methods
Our aim was to evaluate the changes in weight and metabolic parameters as well as the side effects of semaglutide use for weight management in a real-life clinical setting. Retrospective review of data on off-label semaglutide use in a weight management clinic in Athens, Greece, for adults with body mass index (BMI) > 30 kg/square meter with at least 3-month follow-up. Patients with diabetes mellitus were excluded. All patients received standard advice about reducing calorie intake and regular physical activity.
Results
Real-world data analysis included 25 patients (19 females, 6 males) with median age 46 years, weight 106.9 kg and BMI 38. Amongst those, eight patients had BMI 30-35, six 35-40, five 45-50, and six > 45. Four individuals had undergone bariatric operation in the past, while four had received medications for obesity. The most common weight-related comorbidities were dyslipidaemia (19/25), prediabetes (15/25), non-alcoholic fatty liver disease (12/25), obstructive sleep apnoea (5/25), depression (5/25) and hypertension (4/25). The median 12-week percentage weight loss was 7.1%, with 72% and 12% of patients achieving > 5% and > 10% weight loss, respectively. The median 24-week percentage weight loss was 13.5% with loss exceeding 5% and 10% of the baseline weight in 87% and 68% of cases, respectively. At week 24, half patients received weekly semaglutide dose of 2.0 mg and the remaining 1.0 mg due to cost reasons. The median percentage weight loss was similar, 12.7% for 2.0 mg and 13.8% for 1.0 mg dose. After 24-week semaglutide therapy, median fasting glucose decreased from a median baseline of 5.7 mmol/l to 5.0 mmol/l. The discontinuation rate was 5%, with only one case of semaglutide withdrawal due to protracted vomiting, while pancreatitis and gallbladder disease were excluded. All other patients had no or minor gastrointestinal symptoms.
Discussion
Real-world data confirm the effectiveness and safety of semaglutide for weight management. Semaglutide could herald a new era in the treatment of obesity, provided public funding ensures wide patient access. This case series reports great potency of semaglutide at the lower dose of 1.0 mg which needs to be explored further.

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Chronic inflammation linked to obesity has a negative impact on serum glycated albumin levels, but not glycated hemoglobin levels

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Background
Glycated albumin (GA) and glycated haemoglobin (HbA1c) measurements have been used to track the long-term glycemic management of diabetic patients. Other than glycemia, there are known influences on both glycated proteins. In obese, non-diabetic children, GA levels have been found to be low, while in adult diabetic patients, GA levels have been found to be adversely correlated with body mass index (BMI). The causes of the link between obesity and GA are still unknown, though.
Objectives
This research aimed to see if GA and HbA1c were independently correlated with BMI and the inflammation-related inflammatory marker plasma high-sensitivity C-reactive protein (hs-CRP), which is related to obesity.
Material and Methods
This study included 215 non-diabetic participants, of which 150 had normal glucose tolerance and 65 had impaired glucose tolerance. Age, BMI, 2-hour glucose, fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), and hs-CRP impacts on HbA1c and GA were examined. Unpaired Student's t tests or Fisher's exact tests, if applicable, were utilised in statistical analyses to compare two groups. With the help of the StatView software, stepwise multivariate regression analysis as well as univariate regression analysis were carried out to examine the impact of explanatory variables on HbA1c, GA, and the GA to HbA1c ratio (for correction). The F-value for the variables' inclusion in the stepwise multiple regression analysis was set at 2.0, and a P value of less than 0.04 was regarded as statistically significant.
Results
Significant correlations were found between FPG and HbA1c as well as between GA and FPG. While BMI and HbA1c exhibited a substantial positive connection, GA and BMI showed a negative correlation. Plasma hs-CRP was inversely correlated with GA while weakly positively correlated with HbA1c. BMI and hs-CRP were found to be negatively linked with GA but not with HbA1c by stepwise multivariate regression analysis.
Conclusion
This research indicate that in nondiabetic patients, BMI and hs-CRP were independent unfavorable hazards for GA but not for HbA1c. Lower blood GA levels in proportion to glycemia are caused by obesity and the associated chronic inflammation, but not by HbA1c levels.

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What role does the Very Low-Calorie Ketogenic Diet (VLCKD) in obesity-related kidney complications?

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Background
Obesity can damage kidney via directly, through the production of pro-inflammatory adipocytokines, and indirectly due to systemic complications. Several strategies are available for weight loss (lifestyle, anti-obesity drugs and surgery therapy), but there are no guidelines to manage subjects with obesity and chronic kidney disease. Very low-calorie ketogenic diet (VLCKD) is an increasingly used tool for weight loss in subjects with obesity. Thus, we aimed to investigate the effects of VLCKD on subjects with obesity and mild kidney failure (MKF).
Methods
A cross-sectional study was conducted on 92 subjects with obesity (35.85 $\pm$ 4.61 kg/m^2; 27M/65F aged 52.03 $\pm$ 11.41 years) that underwent to a VLCKD. Anthropometric parameters and biochemistry data were collected before and at the end of active phase of VLCKD. Glomerular Filtration Rate (GFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Forty-nine subjects had MKF (GFR 60-89 ml/min/1.73m^2) and 43 had

normal kidney function (NKF) (GFR≥90 ml/min/1.73m^2) and were therefore designated as control.

Results

In the entire study population, the average weight loss was -10.67 ± 4.29 % of initial weight, with significant reductions in BMI (from 35.85 ± 4.61 to 32.50 ± 4.35 kg/m^2, $P<0.001$) and waist circumference (from 107.01 ± 11.32 to 99.98 ± 11.42 cm, $P<0.001$) at the end of the active phase of VLCKD. We also reported an improvement of several metabolic parameters: fasting blood glucose, insulin, HOMA-IR, total cholesterol, LDL and triglycerides ($P<0.001$ for all). No clinically relevant variation regarding liver and kidney function were detected. Of note, at the end of the active phase of VLCKD we found out significant reduction of GFR in subjects with NKF (from 104.53 ± 7.30 to 100.76 ± 11.39 ml/min/1.73m^2; $P=0.031$) while a significant increase in subjects with MKF (from 79.33 ± 7.82 to 84.61 ± 11.65 ml/min/1.73m^2; $P=0.001$). Finally, 30.6% of patients with MKF reported normalization of glomerular filtrate after the VLCKD.

Conclusion

Obesity can damage the kidney through alterations in the hemodynamics resulting in glomerular hyperfiltration, proteinuria and, finally, impairment of the GFR. VLCKD on the one hand reduced glomerular hyperfiltration in subjects with obesity with still NKF, and on the other hand improved filtration in those subjects who have already suffered a reduction in GFR. Consequently, VLCKD is a safe and effective tool for obesity-related kidney complications.

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Managing stigma of Adolescents Diabetes in developing nations

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Issues

Adolescent diabetes social stigma in India. Such diabetics needs proper guidance/information/treatment-counselling outlets. This is burning issue in developing-nations like India. Hence we all need to unite & form a comprehensive diabetes care & counselling policy plan at ECE conference. Treatment options must be suitable for developing-nations considering cost of Rx. Incorporating NGO's in such efforts is very effective.

Our Project Methodology

This is a policy paper. Our 10 year-old-NGO started Diabetes education-project in rural India from 2014. we started s education & surveillance project to analyze social & anthropological issues facing those affected by adolescent diabetes. Total 162 adolescents subjects enrolled by Feedback questionnaires to get their feedback on special needs, perceptions, social attitude on diagnosis of diabetes. Factors like community-inhibition, social-ostracism, economic-difficulties, marital discord, non-availability of treatment-guidance centres, lack of trained-staff analysed & draft policy is recommended to Govt-agencies.

Lessons learned

Adolescent diabetes management must include care of nursing & psycho-social needs. Here role of NGO's in diabetes education is very effective in terms of cost-management, better impact & better-compliance of young diabetics. Community mass intervention projects has proven useful in rural communities of resource poor-nations. ECE participants can collaborate with NGO-activists to address this issue. Uniform public health policy needed to implement & expand newer strategies to include broader range of diabetes care-issues.

Recommendations

Promoting dialogue between Government-health-services & NGO's accelerates diabetes education/awareness programs. NGO participation improves cost-efficacy of such initiatives in economically poor populations. This would reduce difficulties faced by young diabetics from Asian countries. It is essential that WHO/ESE makes common guideline manual on this issue affecting developing-countries. We graphically present our NGO's project on diabetes patients education project in four phases to ECE participants.

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P357

Assessment of Western dietary patterns in Georgian population with prediabetes

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A Western dietary pattern, characterized by high consumption of red and processed meat, soft drinks, refined grains, fats and sweets, has frequently been associated with an increased disease risk. However, the distinct association between the nutritional habits and prediabetes has only been scarcely investigated in Western populations. The aim of this study is to underline the relationship and suggest the possible causality between the two. We conducted descriptive survey and formulated specific questionnaire with which we collected the responses of 160 participants BMIs of participants are as follows: 15-18 are 6%; 19-25 are 42%; 26-30 are 22.7%; 30+ are 29.3%. Out of 160 participants 25% eat processed meat twice a week, 14.3% - once a week, 16.25% rarely, 3.12% never, 15.62% every day and 25.62% every other day. 21.9% of the participants consume dairy products everyday, 21.2% every other day, 38.4% twice a week, 8.6% once a week and 7.9% seldom, 2% - never. Regarding seafood 62.3% consumes less than one portion (100-150 grams) during the week, 23.2% consumes 1 portion, 11.3% 2 portions, 2% 3 portions and the remainder 2% more than 3 portions.4.6% of participants consume junk food every day, 25.8% every other, 29.8 % once a week, 8.6% more than once in a month, 18.5% once in a month and 12.6% don't consume at all. About the fruit consumption 31.8% of the participants consume fruit everyday, 32.5% every other day, 17.9% twice a week, 9.3% once a week and 8.6 % seldom. As for portions (200 grams) of vegetables consumed in a day, 9.9% consume more than two portions of vegetables 16.6% 2 portions of vegetables, 38.4% consume one portion, and the remainder 35.1% consume less than one portion of vegetables. 41.7% state that they consume carbonated drinks often; 34.4% consume sometimes, 19.2% consume seldom, and 4.6% never. As for the desserts/pastries, 41.7% of participants consume it every day, 34.4% every other day, 11.3% consume twice a week, 6.6% - once in a week and 6% consume desserts seldom. Given results are suggestive that western dietary patterns (heavily carbonated drinks, processed meats, increased carbohydrates and fats) increase the likelihood of the development of prediabetes.

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P358

Vitamin B12, lipid profile and peripheral diabetic neuropathy in type 2 diabetic patients on Metformin: any association?

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Introduction

Several studies have evaluated the prevalence and impact of metformin induced vitamin B12 deficiency in type 2 diabetes patients. On the other hand, low vit B12 was associated with adverse lipid profile.

Aim

To evaluate the relationship between vitamin B12 deficiency and the lipid profile in patients with neuropathy.

Patients and methods

A cross-sectional study included 123 type 2 diabetic patients treated with metformin. The presence of distal symmetrical polyneuropathy (DSPN) was determined by Toronto Clinical Neuropathy Score (TCSS). Vitamin B12 levels and lipid profile were measured for all participants.

Results

The mean age of participants was 60.99 ± 6.85 years. About 70% were female. The mean duration of metformin use was 14.6±7.27 years with a mean dose of 1923±575.4 mg/day. The mean total cholesterol level was 4.68 mmol/l ±1.2 mmol/l. The mean triglyceride level was 7.71 mmol/l ±0.96. The mean HDL cholesterol level was 1.11mmol/l ± 0.2 mmol/l and the mean LDL cholesterol level was 1.07 mmol/±0.41. There was a difference between the two sexe in the lipid profile ($P<0.005$). Eighty three and a half percent of patients were on statins. The mean dose was 24.13 mg/day with extremes ranging from 10 to 80 mg/day. The mean serum Vitamin B12 level was 353.77 ± 178.22 pg/ml with extremes ranging from 64.47 to 918.4 pg/ml. Eighteen and a half percent of the population had a vitamin B12 deficiency (level <200 pg/ml). There was no correlation between vitamin B12 level and lipid profile. Fifty seven percent of patients have mild neuropathy, 23.5% moderate neuropathy and 19.5% severe neuropathy. There was no correlation between TCSS and Lipid profile. There was no correlation between TCSS and statin dose ($P=0.79$). The mean dose of statins was 23.82 ± 16.75 mg/ day in patients with mild neuropathy,23.10 ± 18.72 mg/day in patients with mild neuropathy and 26.25 ±18.13 mg/day in patients with severe neuropathy.

Conclusion

This study shows no correlation of lipid profile and vitamin B12 level. Statin dose was not associated with the severity of DSPN. Larger studies are needed to clarify the relationship between vitamin B12 and lipid profile.

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P359

Puberty and staturoponderal development in type 1 diabetec patients

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Introduction
Type 1 diabetes affects the puberty and staturopondral development of young diabetics.
Objective
Assess pubertal status in young DT1 patients and determine factors influencing pubertal development.
Materiel and method
Retrospective study involving 89 type 1 diabetics aged $\leq$ 18 years hospitalized in the department C of the National Institute of Nutrition of Tunis between January 2022 and October 2022.
Results
The mean age was 17.5 $\pm$ 5 years with a female predominance of 61%, the onset of diabetes was 9 $\pm$ 2 years. The average HbA1c level was 10.8%. Pediatric transition was noted in 15% of patients. Pubertal delay was observed in 12 girls (15%) and 6 boys (7.5%). The average age at menarche was 12.5 years (10-16), 47% of girls had irregular cycles. A statural delay was reported with 9 boys and 4 girls. Underweight was noted in 18.7% of patients, and overweight in 12% of girls. Pubertal delay was related to glycemic variability ($P=$ 0.02), diabetes seniority ($P<0.02$), and the frequency of hypoglycemia ($P<0.01$). No significant association with insulin regimen and microangiopathies ($P=$ 0.13).
Conclusion
Previous poorly controlled diabetes and hypoglycemia were predictors of delayed puberty. Puberty coincides with the transition period. Pediatrician-diabetologist coordination is needed to limit loss of sight and minimize the impact on growth and puberty.

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P360

Consensus Towards Reassessing Gliclazide for the Place in Therapy Based on Novel Cluster Classification of Diabetes

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Introduction
A novel classification of adult onset DM into five subgroups: Severe Autoimmune Diabetes (SAID); Severe Insulin-Deficient Diabetes (SIDD); Severe Insulin-Resistant Diabetes (SIRD); Mild Obesity-Related Diabetes (MOD); and Mild Age-Related Diabetes (MARD) has been postulated. We aim to formulate a consensus statement towards reassessing gliclazide use based on cluster classification of diabetes mellitus
Methods
A virtual collaborative educational initiative was convened from November-December 2022, through a series of 10 nationwide virtual interactive meetings by leading diabetologists-endocrinologists ($n=150$) at the forefront of diabetes care (RECLIDE Study Group). The cumulative clinical experience was approximately 4,000-man-years, who rated their level of agreement for 13 questions with each item on a 5-point Likert scale. This was preceded by a contemporary evidence-based discussion on the contemporary updates for gliclazide and novel cluster based definition of diabetes. Weighted mean for the Likert scale was calculated and consensus was pre-defined as a score $>$ 50. GraphPad 9.4.0 and ANOVA were used for statistical analysis
Results
The highest agreement score was as follows for the consensus statements: early intervention with gliclazide is associated with reduction in risk factors and better self-management of T2DM (124), gliclazide differs from other sulfonylureas (SUs) in several respects and may provide a suitable option for some patients with T2D (124), gliclazide, among SUs has minimal risk of hypoglycemia (124). This was followed by that, gliclazide is relevant for maturity-onset diabetes of the young (MODY) (115), gliclazide is a relevant SU in T2DM who are inclined to fasting during Ramadan, the distinctive "Structure Activity Relationship' of gliclazide contributes to determine its clinical characteristics (114), gliclazide is relevant for mild age-related diabetes (MARD, cluster 5) (98), relevant for mild obesity-related diabetes (MOD, cluster 4) (62). The highest mean response scores ($\pm$SD, 95% CI) for consensus were for agree (54.7 $\pm$ 19.2, 95% CI 43.1 to 66.4) followed by strongly agree (27.6 $\pm$ 19.7, 95% CI 14.3 to 40.9), neither agree nor disagree (23 $\pm$ 21.5, 95% CI 10 to 36.1), disagree (14.1 $\pm$ 13.5, 95% CI 4.3 to 23.8), and strongly disagree (4.5 $\pm$ 5, 95% CI -3.4 to 12.4).
Conclusions
We observed a high preference for the usage of gliclazide in mild age-related diabetes cluster and mild obesity-related diabetes cluster. Despite the evolution of wide therapeutic armamentarium for management of T2DM, gliclazide still holds a distinctive place in clinical practice. Gliclazide has stood the test of time and it appears that gliclazide would continue to contribute towards the patient-oriented diabetes care.

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P361

Urinary tract infections in patients with diabetes mellitus

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Background and Aim
Patients with diabetes mellitus(DM) are at increased risk of infections, with the urinary tract being the most frequent infection site. High rates of antibiotic prescription, including broad-spectrum antibiotics, for urinary tract infection (UTI) in these patients may further induce the development of antibiotic-resistant urinary pathogens. The aim of our study is to determine the epidemiology of UTI and resistance patterns of bacterial isolates in patients with DM.
Methods
A total of 70 patients with DM presenting UTI admitted to a Tunisian university hospital from 2018 to 2020 were studied retrospectively. Socio-demographic and clinical data, urin culture results and antimicrobial susceptibility patterns of the isolates were collected.
Results
Mean age was 48 years $\pm$15 with female predominance (80%). In female subgroup,57.14% were postmenopausal. Mean body mass index (BMI) was 27.95 $\pm$ 10.5 kg/m^2. Mean HbA1C was 11.3% $\pm$ 3.6. Diabetes was insulin-treated in 70% of cases. Mean duration of diabetes was 10 years $\pm$ 3.7. Of our study population, 68.57% and 11.42% had lower and upper UTI, respectively. UTI was asymptomatic in 50% of cases. The predominant isolate was Escherichia coli (55.71%) followed by klebsiella Pneumoniae (14.28%), Enterobacter cloacae (2.85%), Entercoccus fecalis (1.42%), Acinetobacter (1.42%), Coagulase negative Staphylococcus (1.42%) and Raoutella terrigena (1.42 %). Extended Spectrum Beta-Lactamase Escherichia coli was isolated in 22% of cases and 70% of Klebsiella pneumoniae isolates were resistant to amoxicillin-clavulanic acid, ceftazidime, nitrofurantoin, ceftiraxone, ticarcillin, and piperacillin. The rate of resistance to two or more antimicrobials was 40%. UTI was significantly more prevalent in type 2 DM(67,14% vs 32,86%; $P=$0,04). Upper UTI was significantly associated with female sex (8.5% vs 5.1%; $P=0.002$) and with shorter duration of DM (6.5 years $\pm$5.1 vs 11.5 years $\pm$8.81; $P=0.04$) while age, DM type and treatment and BMI were not significantly associated with upper UTI.
Conclusion
Escherichia coli was the most frequent isolate in both symptomatic and asymptomatic DM patients. More resistant pathogens are a commun finding. Our results are in line with other studies. Investigation of bacteriuria in diabetic patients for UTI is important for treatment and prevention of the development of renal complications.

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P362

Estimation of "Physical Activity Level Equivalence" of Energy Expenditure in Adults with Severe and Complicated Obesity

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Obesity is often framed as a consequence of inadequate physical activity, and patients with severe obesity sometimes attribute their weight gain to immobility and reduced exercise. We sought to compare Total Daily Energy Expenditure (TDEE) in adults with severe obesity to what their predicted TDEE would be at

their Ideal Body Weight (IBW). We conducted a cross-sectional analysis of the Croí CLANN prospective cohort study of patients with severe obesity attending our regional bariatric service. Data on weight, height, age and sex were used to estimate Basal Metabolic Rate (BMR) using the Mifflin-St Jeor formula. A conservative Physical Activity Level (PAL) estimate of 1.4 was used to estimate actual TDEE. Then, the hypothetical PAL required in order for IBW TDEE to match actual TDEE was derived – the "physical activity level equivalent" (PALE). Of 1,102 patients recruited, 67% were female, with a mean age of 46.8 ± 11.9 years, total weight 130.6 ± 25.6 kg, excess body weight was 60.7 ± 22.6 kg, IBW was 69.9 ± 7.7 kg and BMI was 46.7 ± 7.8 kg/m^2. The average theoretical PAL required for patients to achieve their current TDEE if they were at their IBW was 2.03 ± 0.25 units. Estimates of current TDEE in patients with severe obesity, even when conservative estimates of actual physical activity are assumed, suggest that if they were to try to match that TDEE at their IBW, they would need to have long periods of sustained and vigorous physical activity. Whether discussing the "PALE" with patients is helpful or effective in motivational interviewing remains to be determined.

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P363

Bulimia Investigatory Test of Edinburgh (BITE) use in an endocrinology outpatient clinic

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Objectives
To evaluate the prevalence of eating disorders (ED) at an Endocrinology outpatient clinic (EOC); with the use of Bulimia Investigatory Test of Edinburgh (BITE).
Methods
Descriptive analysis of clinical characteristics and BITE scores from patients with suspicion of ED at a first appointment in an EOC with an average of 128 new patients/year. Data was collected from January-2021 to December-2022. The main suspicion criteria were: self-reported anxiety toward food or eating, and/or body dissatisfaction. Results are expressed as means and proportions.
Results
Sixty patients performed a BITE test: 78.33% women, 34.38 ± 14.87 years old, mean body mass index 38.26 ± 5.72 kg/m^2. The vast majority consulted for obesity (88.33%), followed by thyroid pathology (6.66%) and diabetes mellitus (5.01%). More than half (68.33%) received pharmacological treatments: GLP1-R analogues (51.22%), SGLT-2-inhibitors (29.27%), metformin (14.63%), orlistat (2.44%) and others (2.44%). BITE symptom scores were: 20% had an absence of abnormal behaviors (< 10pts), 26.67% had abnormal behaviors, not necessarily bulimia (10-15pts), 18.33% had possible subclinical bulimia (15-20pts) and 35% had possible bulimia nervosa (>20pts). Thirty-seven percent used fasting to attempt weight control, 33.33% used over-the-counter weight-loss pills more than once a day, 6.67% used diuretics, 5% used laxatives, and 3.33% used auto-induced vomiting. Seventy-five percent admitted suffering from binge eating; from occasionally up to several times per day. Regarding severity of abnormal behaviors: 78.33% of patients reported no severity (< 5pts), 18.33% clinically significant severity (5-10pts) and 3.33% a high degree of severity (>10pts). A subgroup analysis for adolescents 16-21 years old ($n = 16$), showed similar results for general clinical characteristics and BITE symptom scores but with higher severity scores: low in 62.5%, significant in 31.25% and severe in 6.25%. Twenty-nine (48.33%) patients were referred to a psychiatry ED unit for diagnosis and treatment. Twenty-two received a psychiatric diagnosis: binge-eating disorder 11.67%, adaptive disorder 10%, major depression 8.33%, not-otherwise-specified ED 5% and bulimia nervosa 1.67%. The referral was proposed and refused by 19.44% of patients.
Conclusions
A high frequency of anxiety related to food or eating and body dissatisfaction were present in this sample. After BITE screening about half of these patients were referred to an ED unit. A significant number of patients refused the referral, possibly in relation to stigma. These results highlight the importance of ED screening at EOCs and the need for multidisciplinary care teams. Prospective studies are required to evaluate the best practices for screening protocols and patient outcome optimization.

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P364

Metformin Ameliorates Fatty Liver Disease in A High-Fat Diet-Induced Obese FVB/N Mouse Model

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Objectives
Previous studies have shown that metformin can reduce high-fat diet (HFD)-induced body weight gain and fat accumulation in the liver. However, the results obtained in animal models regarding the implication of metformin in the modulation of other whole-body and tissue-specific parameters, are controversial or need to be further explored. Consequently, we aimed to explore the capacity of metformin in modulating glucose/insulin metabolism, liver function, adiposity, circulating hormones and lipids, food intake and energy expenditure in HFD-induced obese mice using a different inbred strain, FVB/N, which has been demonstrated to be a suitable and complementary model for diet-induced obesity (DIO) studies.
Materials and methods
Orally administered metformin (250 mg/kg/day) was used in HFD-induced obese FVB/N mice. The effects of metformin on body weight gain and composition, glucose/insulin metabolism, liver physiology, growth hormone and IGF1 axis and hepatic transcriptional regulation were analyzed using animals fed a low-fat diet (LFD) as control.
Results
HFD-fed mice exhibited significantly increased body weight compared to LFD mice, which was accompanied by the proportional increase in total fat mass as assessed by NMR. The observed increase in body weight was due to higher caloric intake. HFD consumption led to an increase in insulin and a non-significant increase in glucose. HFD-fed mice also exhibited impaired glucose tolerance, although no alterations in insulin tolerance were observed. Metformin treatment induced unexpected metabolic effects in HFD-fed mice, with no significant impact on LFD-fed mice. Specifically, metformin treatment did not induce changes in body weight, food intake, body composition, or fasting glucose under HFD or LFD conditions, whereas only a decrease in insulin was observed in metformin-treated HFD mice. However, a substantial effect was observed at the hepatic level as metformin-treated HFD mice exhibited a significantly lower proportion of hepatic steatosis, inflammation and necrosis, while LFD mice exhibited a more inconsistent role. These changes were accompanied by changes in the expression of genes involved in the control of gene expression, suggesting possible biomarkers in the development of steatosis and/or response to metformin.
Conclusion
In animal models, metformin exerts a potent role in the prevention and/or development of liver pathologies, although its effect on other metabolic parameters is highly dependent on the genetic background of the animals and their metabolic state.

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P365

Metabolic abnormalities in adult population with spinal muscular atrophy

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Background
Spinal muscular atrophy (SMA) is hereditary, degenerative, neuro-muscular disease of lower motor neurone that leads to muscle weakness and atrophy. Several metabolic disturbances such as impaired glucose tolerance (IGT), insulin resistance (IR), hypoglycaemia and dyslipidaemia can be present. Most studies were done in children, with more severe forms of SMA. We aimed to assess body composition, IR, glucose and lipid metabolism in adult patients with SMA type 2 and 3.

Material and methods
We designed a cross sectional study consisting of 29 SMA type 2 and 3 (18 (62.1 %) males and 11 (37.9%) females) of median age 44 (30-51.5) years. Anthropometric measurements were performed. Morning blood samples for total cholesterol, LDL, HDL, TG, ApoB, Lp(a), HbA1c and IGF-1 were collected. Blood glucose and insulin were measured during 75 g oral glucose tolerance test (OGTT). Body mass index (BMI) and HOMA-IR were calculated. Body composition was measured with bioimpedance.
Results
BMI was <30 kg/m2 in 25 (86.2%), 30-35 kg/m^2 in 3 (10.3%), >35 kg/m^2 in 1 (3.4%). Increased body fat (women >35%, men >25%) was present in 22 (75.9%) patients. 18 (81.8%) patients with BMI <30 kg/m2 had increased body fat. Normal glucose metabolism was present in 8 (28.6%), isolated IGT in 9 (32.1%), impaired fasting glucose and IGT in 2 (7.1%), diabetes in 9 (32.1%). Fasting hypoglycaemia was recorded in 1 patient (3.6%). Insulin resistance (HOMA-IR>2) was present in 16 (55.2%) patients. Only 1 (3.6%) patient had HbA1c>6.0%. Total cholesterol was increased in 20 (69.0%), LDL in 24 (82.8%), TG in 10 (34.5%), HDL was low in 12 (41.4%). ApoB and Lp(a) were increased in 3 (10.7%) and 8 (28.6%) respectively. IGF-1 correlated with body fat (Spearman's rho -0.547, $P=0.002$ and -0.582, $P=0.001$ respectively).
Conclusions
BMI is not suitable for assessing obesity. Body composition should be measured, as in our population 81.8% of patients with BMI <30 kg/m^2 had increased body fat. Majority of patients have glucose metabolism abnormalities, almost a third fulfils criteria for diabetes. OGTT should be done in all patients with SMA. In children hypoglycaemia is common and usually asymptomatic. Continuous glucose monitoring could add additional information to hypoglycaemia in adults. The most common dyslipidaemia is increased LDL cholesterol. Emerging treatments such as nusinersen, risdiplam and onamsenogene abeparvovec will change course of the SMA, so interdisciplinary approach with inclusion of endocrinologists and appropriate assessment of cardiometabolic risk factors is necessary.

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P366

Assessing Foundation Doctors knowledge on the use of Sodium-glucose cotransporter 2 (SGLT2) Inhibitors: A Quality Improvement Project

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Introduction
Sodium Glucose Co-transporter 2 inhibitors (SGLT2i) are a novel class of glucose-lowering therapies that have demonstrated prognostic benefit in the management diabetes, heart failure and renal impairment. National Institute for Health and Clinical Excellence (NICE) guidance recommends offering SGLT2i, in addition to metformin, first-line in individuals with type 2 diabetes (T2D) and chronic heart failure/ established atherosclerotic cardiovascular disease. However, SGLT2i require close monitoring and rarely can result in life-threatening complications including euglycaemic diabetic ketoacidosis. Therefore, foundation doctors (FDs) (Newly graduated Doctors undertaking the two years foundation training programme) should be competent in their use and early identification of side effects.
Aim
We conducted a quality improvement project to assess FDs' knowledge on the use of SGLT2i, provide educational material and thus improve patient care at Northwick Park Hospital (NPH).
Method
A questionnaire was designed within the department of Endocrinology encompassing 4 key domains including initiation, indications, benefits, and side effects of SGLT2i. FDs (FY1/ FY2) were invited to complete the initial questionnaire between October-November 2022. Within the second cycle, we designed and delivered educational material. This was by a re-audit.
Results
Of 80 FDs at NPH, 32 individuals completed the initial questionnaire. 40%($n=13$) were able to recall the indications of SGLT2i and 44%($n=14$) were well-informed on cardiovascular and renal benefits. 56%($n=18$) were aware of the appropriate eGFR prior to initiation. 56% ($n=18$) could recollect stopping SGLT2 inhibitors during acute illness whilst only 16%($n=5$) were aware of management of euglycaemic ketoacidosis. 59%($n=19$) appreciated the low incidence of hypoglycaemia. Overwhelmingly, 75%($n=24$) of individuals received no prior formal education on SGLT2i. Therefore, we delivered a formal teaching session specifically targeted at FDs. Individuals completed the same questionnaire post-teaching, and 38 responses were collated. Ability to recall indications for use of SGLT2i increased to 74%($n=28$) and 66%($n=25$) were now aware of the beneficial cardiovascular and renal outcomes. 74%($n=28$) could identify the safe eGFR range for commencing SGLT2i. 95%($n=36$) appreciated importance of stopping SGLT2i in periods of acute illness whilst 74%($n=28$) were confident on management of euglycaemic ketoacidosis.
Conclusion
This quality improvement project demonstrated a significant knowledge gap amongst FDs on SGLT2i. By providing focused and targeted educational initiatives, we have demonstrated an improvement in knowledge across all four essential domains. To ensure sustainability, we propose FDs nationally should receive bi-annual teaching sessions on the ever-evolving field of managing T2D.

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P367

Diabetic keto-acidosis secondary to sodium glucose co-transporter inhibitors: single-centre experience

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Background
SGLT-2 inhibitors (SGLT-2i) are used in treatment of type 2 diabetes mellitus (T2DM) through increasing urinary glucose secretion. Cases of euglycemic and hyperglycaemic diabetic ketoacidosis (DKA) have been reported in literature in patients using SGLT-2i. Increased glucose urinary excretion promoted by SGLT2i, decreases the production of insulin. In turn, lipolysis and ketone production increase predisposing the patient to developing DKA. It is

Table 1 (Abstract P367) Comparison of CGM metrics before and after AID initiation, n = 185

	Before AID Initiation	After AID Initiation	P value
CGM wear time,%	81.25 ± 16.9	88.44 ± 12.71	<0.001
CGM data, days	76.39 ± 18.8	81.11 ± 16.47	0.002
Mean sensor glucose, mg/dl	167.57 ± 29.23	150.32 ± 18.36	<0.001
Glucose management indicator(GMI),%	7.3 ± 0.7	6.90 ± 0.44	<0.001
SD	59.40 ± 13.17	49.16 ± 10.12	<0.001
CV,%	35 ± 5	33 ± 4	<0.001
Time below range, <70 mg/dl(TBR),%	3.23 ± 3.33	1.97 ± 1.98	<0.001
Time between 54-70 mg/dl(TBR2),%	0.65 ± 1.03	0.36 ± 0.5	<0.001
Time below 54 mg/dl(TBR1),%	2.58 ± 2.39	1.62 ± 1.52	<0.001
Time in range, 70-180 mg/dl(TIR),%	58.95 ± 17.29	73.56 ± 11.66	<0.001
Time above range, >180 mg/dl(TAR),%	37.81 ± 18.29	24.47 ± 12.18	<0.001
Time between 181-250 mg/dl,(TAR1),%	24.99 ± 8.92	18.87 ± 7.75	<0.001
Time above 250 mg/dl(TAR2),%	12.83 ± 11.26	5.60 ± 5.15	<0.001
GRI	48.66 ± 21.81	29.01 ± 13.01	<0.001
GRI-Hypoglycemia component	2.72 ± 2.85	1.65 ± 1.68	<0.001
GRI-Hyperglycemia component	25.32 ± 14.52	15.03 ± 8.52	<0.001

hypothesised that SGLT2i, stimulate a cells of the pancreas, increasing the release of glucagon. The increased glucagon levels, further stimulate B-oxidation and ketone body production. In our case series we aim to describe the risk factors, demographics associated with development of SGLT-2i associated DKA and the course of disease in such patients.

Methods

All the T2DM patients with diabetic ketoacidosis on SGLT-2i who presented to the emergency department of a large hospital between Dec 26th 2018 and Jan 1st 2023 were included in the study.

Results

Ten patients were included in the study. Patient demographics are summarised in Table 1. All patients had confirmed T2DM, with negative GAD and anti-islet antibodies. Five patients were taking Canagliflozin, four-Empagliflozin, one-Dapagliflozin. Mean blood ketone level on admission was 4.18 mmol/l (2 St.Dev. $\pm$0.274) and venous blood gas pH was 7.088 (2 St. Dev. $\pm$0.155). Blood glucose on admission ranged from (4.7 to 28 mmol/l). Most common symptom at presentation was vomiting ($n=5$). Other common symptoms at presentation were abdominal pain ($n=2$), shortness of breath ($n=2$) and lethargy ($n=2$). Four patients had concurrent illness at presentation: urosepsis, recent knee surgery, community acquired pneumonia and acute coronary syndrome. All patients were treated with sliding scale, 1 patient was transferred to ITU, 1 required HDU support and 1 passed away from a cardiac arrest in ED. Mean duration of hospital stay was 5.3 days (2 St. Dev: 2.46 days).

Discussion

Diabetic ketoacidosis secondary to SGLT2i is a known side effect. In our cohort, we found 3 patients presenting with hyperglycaemia. DKA with SGLT2i is not uncommon, especially with intercurrent illness. Therefore patients on this therapy should be encouraged to monitor their blood ketone levels even if their blood glucose levels are within range.

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P368

LMF1-associated Chylomicronemia Syndrome

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Introduction

Familial Chylomicronemia-FC syndrome is characterized by severely elevated triglyceride levels, i.e., levels of TG above 1000 mg/dl. Monogenic etiology is associated with a small but a significant fraction of Familial Chylomicronemia (FC) Syndrome cases, which is mainly attributed to a few genes, that are involved in Lipoprotein Lipase activity *(LPL / LMF1 / APOC2 / GPIHBP1 / APOA5)*. Bi-allelic variants in these genes cause this rare Autosomal Recessive disorder with a prevalence of ~1 to a million. We herein report a case of a 51year old male, diagnosed with FC syndrome due to a homozygous pathogenic variant in the *LMF1* gene, and the clinical implications of this diagnosis.

Case description

A 51 years old male of consanguineous Jewish Yemenite ancestry, has been investigated in the Endocrinology Clinic due to recurrent pancreatitis. He was diagnosed with severe hypertriglyceridemia (TG levels up to 2300 mg/dl). His past medical history includes type 2 diabetes mellitus and complex PTSD. No family history could be retrieved. Initial treatment included a combination of fibrates, statin, ezetimibe and omega3 fatty acids. The patient was instructed to avoid alcohol, and a strict dietary-fat restriction. Despite good adherence to this treatment, triglyceride levels remained high, around 700mg/dl, and he continues to suffer from mild episodes of pancreatitis that reduce his quality of life.

Molecular investigation

Homozygous *LMF1* c.1391G>A p.Trp464* (RefSeq NM_022773), classified as "Pathogenic" according to the ACMG guidelines.

Discussion

Involvement of LMF1 gene by loss-of-function mechanism has been initially reported in 2007 [Péterfy *et al*]. *LMF1* gene encodes a transmembrane protein, which is involved in the maturation of lipoprotein lipase (LPL) and hepatic lipase in the endoplasmic reticulum. The *LMF1* variant diagnosed in our patient, was previously described (doi: 10.1210/jc.2009-0594). Functional analysis of this variant revealed significantly reduced expression and activity of LMF1 protein. The clinical presentation of our patient is consistent with the molecular diagnosis of Lipase Deficiency (OMIM #246650). Due to lack of improvement on current available treatments, he is a candidate for treatment with Volanesorsen-, a second-generation 2'-*O*-methoxyethyl (2'-MOE) chimeric antisense therapeutic oligonucleotide, that decreases plasma apolipoprotein C3 and triglycerides (TG) levels through LPL-independent pathways. We suspect that the rarity of this syndrome is partly due to underdiagnosis, and the availability of Next generation sequencing will improve our diagnosis and treatment options for our patients. Our hope is to offer personalized treatment based on the specific molecular diagnosis.

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P369

Impact of exenatide on weight loss and eating behavior in adults with craniopharyngioma-related obesity: the Cranioexe randomized placebo-controlled trial

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Background

Hyperphagia leading to craniopharyngioma-related obesity (CRO) is a common and serious sequel of treatments of craniopharyngiomas. The few therapeutic approaches that have been tested until now for the control of eating behaviour and weight have poor efficacy. Glucagon-like peptide-1 (GLP-1) analogues might be an option.

Methods

This multicentre, randomised, double-blind superiority trial was conducted in France. Adults with CRO (BMI $>$ 30 kg/m^2) without sign of recurrence in the past year were included. After a 4-week run-in period with a lifestyle intervention, participants were randomized (1:1) to receive exenatide 5 µg x 2/day for 4 weeks increased to 10 µg x 2/day for the following 22 weeks or placebo injected subcutaneously twice a day, using a computer-generated randomisation sequence. The lifestyle intervention (hypocaloric diet and regular physical activity) was maintained during the 26-week follow-up. The primary outcome was mean change in body weight (kg) at week 26 in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, NCT02860923.

Findings

Between January 2017 and February 2018, 41 participants were subjected to an intensive lifestyle intervention and randomly assigned to exenatide ($n=20$) or placebo ($n=20$). At week 26, weight decreased from baseline by a mean of - 3.8 (SD 4.3) kg for exenatide and -1.6 (3.8) kg for placebo. Adjusted mean treatment difference was -3.1 kg (95% CI -7.0 to 0.7, $P=0.11$) in favor of exenatide. The estimated treatment difference from baseline to week 26 was -2.3 (95% CI -4.5 to -0.2) for reduction of hunger score, -1.2 (95% CI -3.2 to $+0.8$) for reduction of disinhibition score and – 8.1 cm (95% CI -21.1 to 4.9) for reduction of waist circumference in favor of exenatide. Restriction score and quality of life did not significantly differ between groups. A heterogeneity in the response to therapeutic intervention was observed. Adverse events occurred in 19 (95%) participants in the exenatide group vs 14 (70%) in the placebo group.

Interpretation

The results of our study show that both lifestyle intervention and exenatide have an impact on body weight. Exenatide was not demonstrated superior to placebo, when combined with intensive lifestyle interventions. The heterogeneity in response suggest that GLP-1 receptor agonists might be an additional option in targeting both body weight loss and eating behavior, in a subset of CRO population.

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P370

Characteristics of carbohydrate metabolism and insulin resistance in patients with chronic pyelonephritis depending on the phenotype of latent autoimmune diabetes in adults

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Background
Chronic pyelonephritis (CP) is a common kidney infection complication in patients with diabetes mellitus and one of the main reasons of chronic kidney disease in diabetic patients.
The objective
Of the study was to determine the features of the carbohydrate metabolism and insulin resistance in patients with CP depending on the phenotype of latent autoimmune diabetes in adults (LADA).
Methods
28 patients with LADA and CP were examined, as well as 25 representatives of the control group. The patients were divided into two groups by the phenotype of LADA: 19 patients with LADA1 and 9 with LADA2. We studied fasting plasma glucose levels, glycated hemoglobin (HbA1c), HOMA-IR index and anthropometric indicators: body mass index (BMI), waist circumference (WC) and waist circumference to hip circumference ratio (WC/HC).
Results
Fasting plasma glucose level was 40.3% higher in patients with LADA1 than in the control group ($P<0.001$), in LADA2 it was 2 times higher ($P<0.01$). The HbA1c indicator was 83.6% higher in LADA1 and 55% higher in LADA2 compared to the control ($P<0.001$), respectively. HOMA-IR index was registered 1.6 times lower in LADA1 group compared to the control ($P<0.05$), but 2.2 times and 3.4 times higher in LADA2 compared to the control and LADA1 ($P<0.001$). BMI in LADA1 was lower than in the control group by 11% ($P=0.001$); in LADA2 it was higher by 17.8% ($P<0.01$) than in the control group and by 32.5% in relation to LADA1 ($P<0.001$). The WC was lower by 1.3% when comparing the LADA1 and control group ($P<0.05$), in LADA2 – by 34.6% and by 36.4% higher than in the control and LADA1 group respectively ($P<0.001$). The WC/HC was found to be higher by 20.5% in individuals with LADA2 compared to control and by 25% compared to LADA1 ($P<0.001$). In patients with LADA1 positive relationships were recorded between the HbA1c and the age of manifestation of diabetes ($r=0.489$; $P<0.05$). In the LADA2 group negative correlations were found between the fasting plasma glucose and the duration of diabetes ($r=-0.725$; $P<0.05$); HbA1c level and the age of manifestation of diabetes ($r=-0.788$; $P<0.05$); HbA1c and the duration of diabetes ($r=0.690$; $P<0.05$).
Conclusion
Insufficient compensation of diabetes is noted in patients with LADA1 and LADA2 without differences in intergroup comparison, however the degree of insulin resistance and abdominal obesity as main components of metabolic syndrome prevalence in patients with LADA2 which indicates the higher cardiovascular risk in this category of patients.

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P371

Prevalence and Predictive Factors of Painful Diabetic Peripheral Neuropathy in The Department of Endocrinology and Metabolic Diseases of The Uhc Ibn Rochd In Casablanca: About 623 cases

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Introduction
Peripheral neuropathy is one of the most common complications of diabetes. Its prevalence is very different according to the studies ranging from 8 to almost 60%. The symptomatology can be very polymorphic. Its painful form, painful diabetic neuropathy (PDN), is the most common cause of peripheral neuropathy.
Objective of the study
Our objective was to determine the prevalence and factors associated with PDN.
Material and methods
This is a descriptive cross-sectional observational study including 623 patients followed in the endocrinology and metabolic diseases department of the Ibn Rochd University Hospital in Casablanca in a day hospital or in conventional hospitalization between January 2021 and July 2022. The painful diabetic neuropathy was assessed by the DN4 score. Statistical analysis of the data was performed using SPSS version 25.
Results
We included 623 patients, 63.4% of whom were women. The average age of the patients was 51.4 $\pm$ 16.1 years. Diabetes was type 2 for 79.9% of patients. The mean HbA1c was 10.22 $\pm$ 2.53%. Among our patients, 30.8% were obese. The prevalence of PDN was 22.2%. Diabetic retinopathy was the most frequent complication with a percentage of 24.2%. In bivariate analysis, the risk factors associated with PDN were: age $>$ 69 years ($P<0.001$), arterial hypertension ($P=0.005$), dyslipidemia ($P=0.001$), duration of diabetes $>$ 10 years ($P<0.001$), HbA1c $>7\%$ ($P<0.001$), retinopathy ($P<0.001$), nephropathy ($P<0.001$), autonomic neuropathy ($P<0.001$), coronary artery disease ($P<0.001$) and obliterating arteriopathy of the lower limbs ($P<0.001$). In multivariate analysis, the predominant risk factors for PDN were: HbA1c$>$ 7% ($P=0.01$ and Odds ratio at 3.7), retinopathy ($P<0.001$ and Odds ratio at 3.37), autonomic neuropathy ($P<0.001$ and odds ratio at 3.23) and coronary artery disease ($P=0.005$ and odds ratio at 3.47). All of the patients with PDN were put on pregabalin with a good evolution.
Conclusion
Diabetic neuropathy can have an impact on the quality of life of patients, prompting its detection by the DN4 score. Its management must include good glycemic control, management of risk factors and symptomatic treatment of pain.

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P372

Diabetic ketoacidosis as first presentation of diabetes mellitus in a subject with Friedreich' ataxia. A case report and review of literature

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Introduction
Friedreich ataxia (FA) is a multisystem autosomal recessive disease with progressive clinical course involving the neuromuscular and endocrine system. Individuals with FA have an increased risk of developing diabetes. In FA-associated diabetes, both insulin deficiency and insulin resistance have been reported. We present a case with FA, presented with diabetic ketoacidosis (DKA) as the first presentation of diabetes mellitus.
Case Presentation
We present a case of 40-years-old male who presented to emergency unit with DKA. It was not known to be diabetic before. He had a 6months history of physical weakness, weight loss, polyuria-polydipsia syndrome, dry mouth. For the last 3 days, he complained of constipation, chesty cough, dyspnea, abdominal pain, vomiting-after having a viral infection. The patient was diagnosed with FA, muscular dystrophy at the age of 15. No family history of diabetes mellitus. His physical examination revealed, coma, dry and pale mucous membranes and skin, bilateral basal crepitant rales, on lungs auscultation. Abdomen soft but painful on palpation, peripheral edema more pronounced in superior extremities. Laboratory tests showed: Hyperglycemia, severe metabolic acidosis, urinary ketones. Leukocytosis with neutrophilia. Hyperuricemia, hypoalbuminemia. Increased level of urea and creatinine. Very low C-Peptide level, but the immune markers typical of type 1 diabetes were negative. High level of HbA1c. We concluded with the diagnosis: DKA and diabetes mellitus for the first time in a subject with FA. He was treated with insulin, liquids and electrolytes, nasal oxygen, diuretics, antibiotics, vitamins, anticoagulant until the stabilization of acid basebalance, glycaemia and lungs infection. After that, the patient was noted to have difficulties with standing, inability to walk, difficulty in speaking and reduced hearing because of FA. The ECG showed sinus rhythm, T waves negative in almost connections. Head MRI: atrophic changes of the brain. The patient discharged after 12 days, keeping diabetes under a good control with insulin, helped by his family members.
Conclusion
The association of diabetes mellitus with Friedreich's ataxia has been reported from time to time in the literature. DKA can be the presentation of diabetes mellitus in a patient with FA. The physicians must be aware about it to diagnose diabetes in time and to treat it early without reaching DKA, this life-threatening situation.

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P373

Glycemic control in Type 1 Diabetes patients using multiple daily insulin injections (MDII) vs continuous subcutaneous insulin infusion (CSII)

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Objective
Glycemic control of patients with type 1 diabetes is mainly based on insulin administration. The ongoing technological developments in continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion (CSII) provide new treatment strategies, with better glycemic control. This study assessed the clinical impact of two treatment strategies in adults with type 1 diabetes (T1D): multiple daily insulin injections (MDII) vs continuous subcutaneous insulin infusion (CSII).
Material and methods
This is a retrospective cohort study of 70 patients with type 1 diabetes (PWT1D), after their care has been transferred to two Diabetes centers, one in Athens and one in Thessaloniki, between January 2017 and May 2021. PWT1D were divided according to insulin administration mode i.e. MDII ($n=40$) or CSII ($n=30$). They were trained in carb counting and were offered continuous glucose monitoring (CGM), either real-time (rtCGM), or intermittently scanned (isCGM). Among patients on CSII, 43.3% used rtCGM and all the other patients used isCGM, due to prescription restrictions. HbA1c was measured at the beginning of patient care and after 6 to 12 months of monitoring. CGM data were analyzed according to predefined glycemic indices: percentage of time within range (TIR), below range (TBR), and above glucose target range (TAR), also at the beginning and after 6 to 12 months of follow-up.
Results
Baseline characteristics of the two groups of PWT1D did not differ in median age and duration of disease ($P>0.05$), except for BMI which was lower in those using MDII (25.05 ± 5.97 vs 28.28 ± 5.92 kg/m^2, $P=0.028$). Baseline HbA1c was 8.3% for MDII users and 8.34% for CSII ($P=0,863$). After 6-12 months of monitoring, HbA1c decreased to 7.5% in both groups, with a non-significant difference ($P=0.863$). TIR was also similar for both groups (MDII 55.58%, SD=0.95 vs CSII 58.94% SD=16.64, $P=0.418$). Conversely, TBR was significantly lower for patients on CSII (2.64 ± 3.80 vs 5.66 ± 4.94%, $P=0.001$). CGM use was more consistent in CSII users than in MDII (58.94 ± 1.10 vs 55.58 ± 17.04, $P<0.001$).
Conclusions
Care of patients with type 1 diabetes in Diabetes Centers combined with continuous glucose monitoring results in HbA1c decrease. The utilization of MDII or CSII does not seem to impact HbA1c reduction degree or TIR. Patients on CSII exhibit fewer hypoglycemic episodes and TBR compared to those on MDII.

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P374

The Effect of Diabetes Mellitus on the Outcome of Sars-Cov-2 Infection

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Introduction
Infection from the severe respiratory distress syndrome coronavirus 2 (SARS-CoV-2) virus may present as mild disease or as severe disease with high mortality. Although the majority of patients infected by the virus have a good prognosis, chronic diseases, such as diabetes mellitus (DM), especially in older adults may be a risk factor for a worse outcome. DM is a frequent comorbidity in patients with COVID-19.
Aim
The aim of the present work was to study the relationship between DM and SARS-CoV-2 infection and the effect of DM on disease outcome and the duration of hospitalization.
Methods
A cohort of patients were studied with confirmed COVID-19 infection examined at the Department of Emergency Medicine, Venizelion General Hospital, Heraclion, Crete during the days on duty (15 days/month) from the 1st of March until the 31st of August 2021.
Results
A cohort of 776 adult patients, 384 female and 391 male, medial age 47 years were included in the study. Within the group of patients examined at the Department of Emergency Medicine 129 (16.62%) had DM. Within the cohort of 129 DM patients, 70 (54.26%) male 59 (45.74%) female, with acute SARS-CoV-2 infection 106 survived and 23 died (17.83%, $P<0.001$). Within the group of DM patients examined at the Department of Emergency Medicine with acute COVID-19 infection 80% needed hospitalization. Within this group of patients with DM and acute COVID-19 infection who were admitted to the hospital 23 patients (17.83%) were transferred to the Acute Care Unit and all unfortunately succumbed to the infection. Mean number of days of hospitalization of the diabetic group in the COVID-19 department was statistically significantly higher as compared to that of the group without DM (10.2 vs 6 days, $P<0.001$).
Conclusions
It appears that DM significantly adversely affects the duration of hospitalization and the outcome of COVID-19 infection. The results of our study are in accordance with those of the literature regarding the effect of DM on the outcome of SARS-CoV-2 infection. Chronic hyperglycemia significantly affects innate and humoral immunity. It appears that DM is an independent risk factor for severe COVID-19 infection.

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P375

Reduction in Diabetes Distress and Improvement in Sleep Quality correlating with Better Glycemic Control Within 90 Days on Fitterfly Diabetes Program

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Background
Managing the relentless requirements of diabetes management can lead to an increase in distress among people with diabetes. There is a need for feasibility studies to understand the effectiveness of multi-disciplinary care delivered using digital therapeutics interventions to provide effective glycemic control along with improved overall well-being of individuals. The study aims to evaluate the feasibility and effectiveness of the Fitterfly diabetes program to improve diabetes distress and sleep quality during the 90 days period of lifestyle change.
Methods
175 participants with T2DM enrolled in Fitterfly diabetes program for 90 days across India (74 females and 101 males with mean age $=49.79\pm12.2$ years) were analyzed. Virtual consultations with psychologists were provided to each participant along with expert-led care including nutritionists and physiotherapists. Diabetes Distress Scale (DDS) and Pittsburgh Sleep Quality Index (PSQI) were used to assess diabetes distress and sleep quality respectively. All the outcomes were assessed at the beginning and end of the program. Data was analyzed on SPSS. Unadjusted correlation analysis was done using the spearman method.
Results
Diabetes distress was reported in 46.28% (81/175) of participants. Sleep quality was poor among 80.00% (140/175). Towards the end of the program, a significant median reduction was seen in DDS score by 0.50 (0.20, 1.20) from a baseline score of 1.90 (1.40, 2.60) ($P<0.01$). PSQI score significantly reduced by 3.00 (1.00, 6.00) from a baseline score of 5.00 (3.00, 8.00) ($P<0.01$). HbA1c levels significantly reduced by 1.20 % (0.50, 2.30) from 8.00% (7.20, 9.70) ($P<0.01$). Fasting blood sugar levels also significantly reduced by 25.00 (7.00, 55.00) mg/dl from a baseline score of 142.00 (121.00, 177.00) mg/dl ($P<0.01$). Reduction in DDS score was found to be significantly correlated with reduction in HbA1c ($r=0.193$, $P=0.01$) and reduction in fasting blood sugar ($r=0.238$, $P=0.001$). After completion of the program, improvement in PSQI score was found to be correlated with reduction in fasting blood sugar ($r=0.178$, $P=0.01$).
Conclusion
Significant reduction in diabetes related distress and improvement in glycemic control and sleep quality was observed after completion of the Fitterfly diabetes program. Reduction in DDS might play a role in improvement of glycemic control. The study showed that holistic management using a multidisciplinary team through digital therapeutics can help in improved health outcomes in people with diabetes.

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P376

Transition to adult care in type 1 diabetes. A single center retrospective study

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Background
Moving from childhood to adulthood is a challenging process for individuals with type 1 diabetes (T1D), transition has been defined as the planned movement from pediatric to adult department.
Aim
To assess glucometabolic control, prevalence of autoimmune disorders, and use of glucose sensors in patients with type 1 diabetes after transition to adult care.
Methods
We retrospectively evaluated HbA1c, prevalence of patients using real-time (rt) or intermittently-scanning (is) continuous glucose monitoring (CGM) and prevalence of autoimmune diseases at the time of first evaluation in the adult clinic (baseline) and at the last follow-up. HbA1c values were additionally analyzed in a subgroup of patients at 1 and 3 years after transition.
Results
A total of 132 patients were enrolled between January 2017 and January 2023. We excluded patients without T1D and HbA1c at first visit (final cohort $n=102$). Median age at transition was 21 years (interquartile range-IQR 20-22 years) and age of diabetes onset was 9 years (IQR 6-11 years). Sex was evenly distributed (50% females). At baseline, the median HbA1c was 56 mmol/mol (IQR 51-67 mmol/mol). The prevalence of autoimmune diseases was 32% for autoimmune thyroiditis, 16% for celiac disease and 5% for other autoimmune disorders. Multiple daily injection therapy was prevalent (69% of the patients), as opposed to insulin pump (31%). Among those, 13% had advanced hybrid closed loop system. With regard to glucose monitoring, 48% of patients were under capillary monitoring, 18% had isCGM, and 34% rtCGM. After baseline visit, 87% of patients had at least one follow-up visit and the median duration of follow-up was 30.4 months (16.7-46.7 months). At the last follow-up, the median HbA1c was 57 mmol/mol (49-64 mmol/mol) and 37% of patients had HbA1c $\leq$ 53 mmol/mol, while 21% had HbA1c $\leq$ 48 mmol/mol. The analysis of the subgroup of patients at 1 ($n=60$) and 3 years ($n=28$) showed no significant difference in HbA1c compared with baseline HbA1c. An increase in sensor use was found, with 20 new CGM devices positioned, against 3 CGM removed. Autoimmune screening at last follow-up resulted in new diagnosis of 5 autoimmune thyroiditis and 2 autoimmune atrophic gastritis.
Conclusion
Patient with type 1 diabetes showed a stable metabolic control of diabetes after transition to adult care, which occurred in spite of an increase in prescription of CGM devices.

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P377

"Skewing of Antimony Mediated Therapy for an Optimal Insulin Secretion During Visceral Leishmaniasis

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Objective
Visceral Leishmaniasis is a macrophage associated disorder for the treatment of which antimony based drug like Sodium Antimony Gluconate has been the first choice in the recent past. About 5 percent of the patients may develop insulin dependent diabetes mellitus. It appears to have a direct action on pancreatic beta cells, resulting in initial insulin release followed by impaired insulin secretion. Within this context we looked into alternate therapies of treatment along with SAG on triggering the CD2 epitope.
Methods
We have evaluated the effect of combining CD2 with conventional antimonial (sb) therapy in protection in BALB/c mice infected with either drug sensitive or resistant strain of Leishmania donovani with 3 million parasites via-intra-cardiac route. Mice were treated with anti CD2 adjunct SAG sub-cutaneously twice a week for 4 weeks. Assessment for measurement of weight, spleen size, anti-Leishmania antibody titer, T cell and anti-leishmanial macrophage function was carried out day 0, 10, 22 and 34 post treatments. Insulin levels were also determined on the same intervals.
Results
The combination therapy was shown boosting signicant proportion of T cells to express CD25 compared to SAG monotherapy. Although, the level of IFN-γ was not statistically different between combination vs monotherapy ($P=0.298$) but CD2 treatment even alone signicantly influuenced IFN- γ production than either SAG treatment ($P=0.045$) or with CD2 adjunct SAG treatment ($P=0.005$) in Ld-S strain as well as in Ld-R strain. The influence of CD2 adjunct treatment was also documented in anti-leishmanial functions in macrophages. Interestingly insulin levels were observed to be optimal on supplementing SAG along with CD2.
Conclusion
SAG along with CD2 could be used as a potential therapy to overcome incidences of Diabetes mellitus during Visceral Leishmaniasis.

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P598

Impact of Setmelanotide Treatment on Weight- and Body Composition–Related Outcomes in Pediatric and Adult Patients With Hypothalamic Obesity

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Background
Hypothalamic obesity (HO) is an acquired form of severe obesity that can occur following surgical resection of or radiotherapy for brain tumors and is often unresponsive to lifestyle modifications or traditional obesity pharmacotherapies. Here, we report weight- and body composition–related findings from a Phase 2 trial of setmelanotide, a melanocortin-4 receptor agonist, in patients with HO.
Methods
A Phase 2, open-label, 16-week trial of setmelanotide in patients aged $\geq$6 to $\leq$ 40 years with HO caused by hypothalamic damage secondary to brain tumor, surgical resection, and/or chemotherapy was performed. Setmelanotide was initiated at 1 or 2mg and increased to 3mg once daily over 2-4 weeks. The primary endpoint was the proportion of patients reaching $\geq$5% body mass index (BMI) reduction from baseline at Week 16. Secondary and exploratory endpoints included changes from baseline in BMI Z score (patients aged $\geq$6 to 18 years), body weight, and waist circumference. Change in body composition, measured by dual-energy x-ray absorptiometry was also assessed.
Results
Eighteen (13 pediatric, 5 adult) patients were included. Tumor types leading to HO included craniopharyngioma, astrocytoma, and hamartoma. All patients adhering to treatment ($n=17$) experienced weight loss, including 2 patients who discontinued because of an adverse event (AE). At Week 16, most (16/18) patients met the primary endpoint (88.9%[90% confidence interval(CI), 69.0%-98.0%]; $P<0.0001$), with mean (standard deviation[SD]) percent changes in body weight of -12.6%(9.1%) and BMI of -14.5% (9.5%); mean(SD) BMI percent change for patients adhering to treatment ($n=17$) was -15.4%. Of 18 patients, 14 achieved $\geq$10% BMI reduction. The mean(SD) BMI Z score change in pediatric patients was -1.3(1.0), and 12 of 13 pediatric patients (92.3% [90% CI, 68.4%-99.6%]; $P<0.0001$) reached $\geq$0.2-point reduction. Across all patients, weight loss was primarily due to reduction in fat mass (mean [SD] change from baseline at Week 16, -7.7 [5.3]kg; -16.4%) rather than lean mass (-3.4 [5.5] kg; -6.5%). The mean(SD) waist circumference change from baseline was -12.0 (5.8)cm (mean[SD] percent change, -10.4%[5.2%]). Treatment-related AEs occurred in 15 patients (83.3%); nausea ($n=11$; 61.1%), skin hyperpigmentation ($n=6$; 33.3%), vomiting ($n=5$; 27.8%), and diarrhea ($n=4$; 22.2%) were the most frequently reported.
Conclusions
Setmelanotide improved BMI, weight, and waist circumference in a heterogeneous population with HO secondary to treatment of 3 different tumor types.

Body composition also improved, with relatively larger reductions in fat vs lean mass.

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P599

The new anthropometric indices and atherogenic indices are correlated with glucose status in women with PCOS

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Introduction

Polycystic ovary syndrome is complex endocrine disorders, characterized by ovulatory dysfunction, hyperandrogenism and polycystic ovarian morphology. Those are lipid abnormalities, hyperinsulinemia, insulin resistance, impaired glucose metabolism, type 2 diabetes mellitus, metabolic syndrome, hyperandrogenism, oxidative stress and infertility. The visceral adiposity index (VAI) is a reliable marker of adipose tissue abnormalities in women with PCOS. A body shape index (ABSI), body adiposity index (BAI) are the other anthropometric indices which have shown correlation with cardiovascular diseases risk and metabolic syndrome risk such as glucose metabolism abnormalities and obesity.

Aim

The aim of this study was to investigate the usefulness of new anthropometric indices such as BAI, VAI, LAP, BRI, ABSI and new atherogenic indices such as TyG index, TyG-BMI index, TyG-WC index in evaluation of glucose parameters in patients with PCOS.

Material and methods

To the study was enrolled of 49 woman with diagnosed PCOS based on the Rotterdam criteria from 2003. Blood samples were taken from patients in the morning, before breakfast. Biochemical parameters (fasting glucose and fasting insulin, glucose and insulin after 60 and 120 minute OGTT, HbA1c, HOMA-IR index) were determined. Anthropometric parameters were measured with the use of standard methods in the morning. These measurements included body weight, height, waist circumference, and hip circumference. After this step anthropometric indices such as BAI (Body Adiposity Index), VAI (Visceral Adiposity Index), LAP (Lipid Accumulation Product), BRI (Body Roundness Index), ABSI (A Body Shape Index), AIP (Atherogenic Risk of Plasma) were calculated. The study conformed to the Declaration of Helsinki and was reviewed by the local bioethics committee

Results

There was observed positive correlation between fasting glucose and analyzed parameters: BAI, VAI, LAP, BRI, TyG index, TyG-BMI index, TyG-WC index ($P<0.05$). There was reported significant positive relationship between glucose after 60 minutes and VAI, LAP, BRI, ABSI, TyG index, TyG-BMI index, TyG-WC index ($P<0.05$). There was observed positive correlation between glucose after 120 minutes and VAI, LAP, BRI, TyG index, TyG-BMI index, TyG-WC index ($P<0.05$). HOMA-IR index was strongly correlated among group of women to all analyzed anthropometric parameters and atherogenic indices ($P<0.05$).

Conclusion

Analyzed newanthropometric indices and new atherogenic indices have demonstrated significant relationship with glucose profile in women with PCOS. These indices may be useful tool in assessing of metabolic disorders in women with PCOS.

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P600

Mitochondrial fitness in mouse Leydig cells is imbalanced by liraglutide upon glucose stimuli

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Metabolic diseases represent a threatening worldwide epidemic that affects the entire body. It is known that metabolic diseases, namely diabetes, and obesity affect spermatogenesis via suppressing testosterone synthesis, inducing oxidative stress and other changes that lead to decreased male fertility. Glucagon-like peptide 1 (GLP1) receptor agonists, like liraglutide, are pharmacological agents recommended to normalize glucose levels in patients with type 2 diabetes mellitus. Recently, these agonists have been approved for the treatment of obesity to reduce body weight in patients without elevated blood glucose levels. However, the effects of liraglutide on male fertility are not fully understood. The main objective of this study was to understand the effect of liraglutide on the function of Leydig cells (LCs) exposed to conditions of hyperglycemia and normoglycemia. For this purpose, we exposed cell cultures of a LCs (BLTK1 cell line) to increasing concentrations of liraglutide (25, 50 and 100 nM), under conditions of normoglycemia (glucose 5 mM) and hyperglycemia (glucose 22 mM). Cellular viability, proliferation, and ROS production were accessed after 48 h treatment. Mitochondria function was accessed by Seahorse XF Cell Mito Stress assay. We observed that none of the concentrations of liraglutide alter the cell proliferation of LCs or induce cytotoxicity, however it induces an increase in the metabolic viability of cells under normoglycemic conditions. Nonetheless, we also observed an increase in oxidative stress caused by all liraglutide concentrations on 5 mM glucose LCs. In addition, mitochondrial bioenergetics is affected, in which liraglutide decreases basal respiration rate, maximal respiration rate, ATP production and proton leak in LCs exposed to hyperglycemic conditions compared to the group of LCs exposed to 22 mM glucose without exposure to any concentration of liraglutide. In conclusion, these results indicate that liraglutide alters the mitochondrial performance of LCs exposed to high glucose concentrations and increases the metabolic viability of cells in normoglycemia. Since mitochondria are essential for cell bioenergetics and for the steroidogenesis that occurs in LCs, it is extremely important in the future to understand the effect of mitochondrial fitness caused by liraglutide on testosterone production and male fertility.

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P601

Development of Exogenous Insulin Antibody Syndrome in a Patient with Type 1 Diabetes Mellitus Using Insulin Analogues

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Introduction

Insulin antibodies, developed in patients treated with exogenous insulin, might affect glycemic control due to their tendency to bind and/or release insulin in an unpredictable fashion. It is reported to be caused by immunoglobulin G-derived insulin antibodies. Insulin antibodies induced by exogenous insulin in diabetic patients is associated with hypersensitivity reactions, glycemic variability mainly with insulin resistance/ hyperglycemia or hypoglycemia. We reported a case of Type 1 diabetes mellitus (T1DM) who developed exogenous insulin antibody syndrome (EIAS) to insulin analogues during follow-up.

Case presentation

A 20 year-old female patient diagnosed as TIDM three months before, had been using insulin aspart and glargine for three months. She weighed 42 kg. Her blood glucose levels were under control and her HbA1c level decreased from 13.9% to 8.6% in two months. Although she followed her diet and increased daily activity, her need for insulin aspart increased (3 U at each meal to 9-12 U), insulin glargine (7 U/d to 16 U/d) in a month. Her blood sugar levels still remained high (fasting plasma glucose were around 200 mg/dl and posprandial glucose levels were around 300 mg/dl). Her insulin regimen was transitioned to insulin detemir and glulisine but, her glucose control could not be achived despite using 2 U/kg of insulin. In suspicion of developing antibodies against insulin analogues, insuline glulisine was changed to regular insulin. Also, the patient's anti-insulin antibody levels were found to be increased than that at the time of diagnosis [30.93→44.62 IU/ml (0-20 IU/ml)]. After this treament regimen, her glucose levels were controlled in doses 0.95 U/kg (8 U regular insulin at each meal and 20 U/d detemir).

Conclusion

The majority of EIAS is reported in patients with type 2 DM and is very uncommon in patients with TIDM. Insulin analogues are known to have lower immunogenicity than animal/human insulin; accordingly, replacement with an insulin analogue is suggested to be an effective treatment of EIAS. However, a recent study by Hattori

et al., found that glargine and aspart were more antigenic than other insulin analogues. Recommended other regimens include glucocorticoids, immunsuppresants and plasmapheresis. Glucocorticoids may induce or worsen ketoacidosis in patient with TIDM. Interestingly, changing insulin regimen to human regular insulin is sufficient to achieve glucose control for our patient.

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P602

Effect of Origanum vulgare L. essential oil on insulin-induced PI3K/Akt signaling and glucose uptake in human adipocytes treated with palmitic acid

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Background
Obesity is strongly associated with insulin resistance (IR). IR at the molecular level may be defined as a diminished activation of PI3K/Akt signaling and its related molecules (IRS-1/Akt/AS160) as well as reduced glucose uptake. Subjects with obesity have elevated plasma levels of saturated fatty acids, such as palmitic acid (PA), which triggers insulin signaling disruption *in vivo* and *in vitro*. Oregano (*Origanum vulgare* L.) is a plant used as a food component worldwide. Interestingly, the main constituents of oregano have shown protective effects on obesity-related dysfunctions. The *Origanum vulgare* L. essential oil (O-EO) contains considerable amounts of phenolic monoterpenes, such as carvacrol and thymol, which may explain the biological activity of the plant. The aim of this study was to assess whether O-EO exposure protects against PA-induced disruption of IRS-1/Akt/AS160 signaling and glucose uptake in human adipose cells.
Methods
Cytotoxicity of a range of O-EO concentrations (0.01–20 µg/ml) was evaluated by MTS assay in *in vitro* differentiated adipocytes from the adipose cell line SW872. Adipocytes were incubated or not with PA for 24 h in the presence or not of O-EO (2-h preincubation), and thereafter stimulated with insulin or vehicle. Thereby, experimental conditions were: control (untreated cells), 0.4 mM PA, 0.1 µg/ml of O-EO, 10 µg/ml of O-EO, 0.1 µg/ml of O-EO (2 h before) + 0.4 mM PA for 24 h, 10 µg/ml of O-EO (2 h before) + 0.4 mM PA for 24 h, and incubated with 100 nM insulin for 10 min. Phosphorylation of Tyr-IRS-1, Ser-Akt and Thr-AS160 were evaluated by Western blot and glucose uptake was assessed using the 2-NBDG analogue.
Results
In SW872 adipocytes, O-EO was not cytotoxic at any concentration assessed. Insulin-stimulated phosphorylation of IRS-1, Akt, AS160 and glucose uptake were not affected by treatment with 0.1 and 10 µg/ml O-EO compared with vehicle-treated cells. PA-treated adipocytes showed a reduction in insulin-stimulated phosphorylation of IRS-1, Akt, AS160 and glucose uptake compared to control ($P<0.05$). Interestingly, these effects were prevented by O-EO treatment.
Conclusion
These findings give new insights into the effect of O-EO ameliorating PA-impaired insulin signaling and glucose uptake in adipocytes. More studies should focus on *Origanum vulgare* L., since might represent a preventive approach in individuals whose circulating PA levels contribute to IR.

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P603

Strategic Designs to identify the best housekeeping genes for the characterization of biomarkers in adipose tissue of patients with obesity and cancer

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Obesity (OB) is caused by an energy imbalance that finally leads to adipose tissue dysfunction, and the appearance of multiple comorbidities, such as certain cancer types, including prostate cancer (PCa), which is one of the leading causes of cancer-related death in men population worldwide. In this context, periprostatic adipose tissue (PPAT) has recently gained increased attention as a key regulator of the pathophysiological relationship between OB and PCa. However, it has been very challenging to identify suitable and useful housekeeping genes (HKGs) in adipose tissue as reference genes for expression analyses in such pathological conditions (OB and cancer) probably due to the constant dynamic state of the adipose tissue. Therefore, the objective of the present work was to identify a set of HKGs in PPAT samples useful in studies focused on the pathophysiological relationship between OB and cancer using PCa as a cancer model. To that end, 15 potential HKGs were bibliographically selected to evaluate their expression levels by quantitative real-time PCR in a PPAT-screening cohort of normoweight (NW)/obese patients with and without PCa (discovery-cohort; $n=20$; 5/group). Then, results were validated using an ample set of samples [validation-cohort; $n=76$; 20/35 PCa patients (with NW/OB), and 6/15 patients without PCa (under NW and OB state), respectively] using a microfluidic quantitative-PCR array (Fluidigm). Stability and HKG suitability were assessed using different software (GeNorm, BestKeeper, and NormFinder). Our results demonstrate that *LRP10*, followed by *PGK1* and *RPLP0* exhibits the lowest variability in expression levels across the discovery-cohort using the two methodological approaches mentioned above. Furthermore, the expression of these three genes ranked with the best scores as HKGs using all the programs by discriminating the samples according to the BMI and the presence/absence of tumors. The same results were obtained when using the validation-cohort. Additionally, the validation of these genes was corroborated by the analysis of genes typically altered in OB and PCa conditions and previously reported to be highly dysregulated in PPAT (e.g., *MMP2, MMP9, LEP*, and *ANGPT1*). Our analyses revealed that the genes with the highest variability were *HMBS*, *PPIG*, and *GUSB* when the pathophysiological relationship between OB and PCa was studied, but these HKGs were valid to discriminate between non-tumor and PCa conditions. Altogether, we can conclude that *LRP10*, *PGK1*, and *RPLP0* should be used as optimal HKGs for gene expression analyses in PPAT from patients with OB and/or PCa.
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P604

Time In Range and Triglyceride/Glucose Index In Type 2 Diabetes with Mafld

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Background and Aims
The metabolic-associated fatty liver disease (MAFLD) is a fatty liver accumulation with metabolic dysfunction (diabetes, overweight/obese, insulin-resistance), a definition more practical for identifying patients with fatty liver disease with high risk of disease progression. The triglyceride-glucose (TyG) index is a marker of insulin resistance. Long-term fasting plasma glucose (FPG) variability is associated with fatty liver content (FLC). Continuous glucose monitoring (CGM)-derived time in range (TIR) is a valuable blood glucose metric and the concept of TIR has emerged from the efforts of diabetes experts to discover a reliable parameter, "beyond HbA1c" to assess glycemic control. Hence, an effective treatment should always target to increase TIR vs Time-below-range (TBR).
Methods
18 Type 2 diabetic patients (M/F:9/9; aged 56 ± 8yr; BMI: 28.3 ± 2.4; duration: 10.2 ± 4,5 yr; FPG: 8.5 ± 1.5 mmol/l; HbA1c:7.9 ± 0.6%) treated with DPPIV/metformin with proven MAFLD were recruited. Antidiabetic therapy was shifted to dulaglutide/pioglidazone. The TyG index was calculated as ln [fasting triglyceride level (mg/dl) × fasting plasma glucose level (mg/dl)/2] and TIR/TBR by real-time (GlucoMen® Day CGM). The primary endpoint was percentage of TIR and TyG index score after 90 days.
Results
A mean TIR (73.1% dulaglutide/pioglidazone vs 68.8% DPPIV/metformin, respectively) or estimated treatment difference (2.96% or 60.9 min/d) and reduced nocturnal TBR (<3.9mmol/l) were observed. TyG index was positively

correlated with HbA1c and negatively with TIR and is a useful tool for assessing glycemic control in T2D patients.
Conclusions
These evidences supported % TIR as an important outcome variable of glycemic control in treatment practice. Compared with HbA1c, CGM-TIR may better capture risk of MAFLD worsening and lower TIR was associated with MAFLD evolution. The TyG index was correlated with the severity of hepatic steatosis (FLC). Dulaglutide/pioglidazone compared with DPPIV/metformin, provided more TIR and time in tight glycaemic range, and reduced TyG in type 2 diabetes.
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P605

A new referral pathway to the multidisciplinary team for inpatients with diabetic foot pathology
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Background
In any given week, 2.5% of diabetic patients have a foot ulcer. In the United Kingdom (UK), there are 7000 lower limb amputations in people with diabetes every year and the annual NHS expenditure on diabetic foot-related healthcare amounts to £1 billion. As per the National Institute for Health and Care Excellence guidelines in the UK, a person with diabetes needs to be referred to an MDT within 24 h of finding a foot ulcer. The National Diabetes Footcare Audit demonstrates better outcomes at 12 weeks for patients with a new diabetic foot ulcer referred early for MDT input. The early identification of patients with a diabetic foot ulcer and a timely referral to the MDT is therefore vital.
Methods
A two-cycle quality improvement project, with retrospective data collection before and after our intervention, was carried out at our hospital with the aim of improving identification of patients and quality of referrals. Those information mainly included ulcer charateristics, past medical history and investigations. An online referral system with a pre-set questions was then introduced along with teaching sessions delivered to the acute medical team. The results were analysed and presented to the endocrinology and diabetes department.
Results
Our results showed that the average monthly number of referrals was 10.3 for the first cycle and 12.5 for the second cycle. The average referral time was 8.3 days for the first cycle and 4.2 days for the second cycle. Size of ulcer reporting improved from 6.5% to 64%, depth of ulcer from 9.7% to 12.0% and position of ulcer from 74.19% to 80.0%. Mention of peripheral vascular disease improved from 9.7% to 20.0%, presence of pulse from 12.9% to 100% and presence of neuropathy from 12.9% to 100.0%. For investigations, mention of microbiology culture results improved from 12.9% to 40.0% and imaging from 22.6% to 60.0%.
Conclusion
There has been an improvement in the time from admission until referral although more work needs to be done to improve the time to within the 24 hour window. The online referral system helped to improve the quality of information of the referral with regards to information on ulcer characteristics, past medical history and investigations. Improved quality of referrals allow for a more efficient MDT functioning and more timely management strategies for patient outcomes. We intend to further continue this project to look at the effect of the referral system on patient outcomes.
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P606

Characteristics of patients admitted to the hospital with diabetes and frailty: preliminary data of an audit in a UK teaching hospital
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Introduction
Older age and diabetes are both risk factors for frailty. Functional decline and disability in older, frail adults with diabetes results in an increased susceptibility to falls and hospital admission. Hypoglycaemia is common and more likely to result in hospital admission in older adults with diabetes and frailty. An Hb_{A1c} of below 7% (53 mmol/mol) is likely to represent overtreatment of hyperglycaemia. JBDS has recommended a review of Hb_{A1c} in the previous 6-12 months for patients with diabetes and frailty. Hospital admission presents an opportunity for clinical evaluation including medication review to deintensify blood glucose lowering treatment. This audit aimed to assess the prevalence and characteristics of patients with type 2 diabetes (T2DM) and frailty admitted to the hospital as an emergency.
Method
We collected data on frailty using the Clinical Frailty Scale (CFS) in older adults with and T2DM admitted to the acute medicine unit(AMU). Their Hb_{A1c} prior and upon admission were noted. Data including gender, body mass index (BMI), medications, and co-morbidities were also collected. Patients were categorized as overtreated if they had an Hb_{A1c} prior to admission of $\leq$ 7%. Chi-squared test, t-test and Mann-Whitney U-test were used to compare categorical data and continuous data between groups, respectively.
Results
Out of 667 patients admitted to the AMU, 67 patients with T2DM and CFS of $\geq$6 were identified representing a prevalence of 10% of acute medical admissions. Fifty-four percent (n=36/67) were female and mean age was 78.3$\pm$9.6 years. The median BMI was 27.5kg/m2 (23.5-32.8) with 36.7%(n=22/60) of normal weight and 63.3%(n=38/60) overweight/obese. Median Hb_{A1c} prior to admission was 6.9%;52mmol/mol (6.0-7.7%;42-61mmol/mol) whilst56.7% (n=38/67) had Hb_{A1c} >7.0% upon admission. Sixty-five percent(n=44/67) had their Hb_{A1c} checked in the last 6 months. Of the older adults with an Hb_{A1c} of <7.0%, 13%(n=5/38) were treated with insulin or sulphonylurea therapy. The overtreated group had lower BMI, required less medications, and had less co-morbidities, compared to patients who were not overtreated.
Conclusion
Our preliminary results showed that older adults with T2DM and frailty represent a high proportion of older adults admitted to hospital acutely. Despite recommendations, one third of patients had not had their Hb_{A1c} measured in the preceding 6 months. Those patients who had an Hb_{A1c} of below 7% whilst taking insulin or sulphonylureas could be considered overtreated and at risk of severe hypoglycaemia. Admission to the hospital presents an opportunity for deintensification of blood glucose lowering treatment in this group.
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P607

SIMBA for Students – teaching endocrinology to pre-clinical medical and pharmacy students through online simulation- a pilot study
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Introduction
Simulation via Instant Messaging – Birmingham Advance (SIMBA) for Students is an online education model used to teach endocrine topics to pre-clinical medical and pharmacy students using simulated clinical cases delivered through WhatsApp and Zoom. In this study, we investigated the efficacy and acceptability of SIMBA for students compared to traditional small-group teaching (SGT).
Methods
These SIMBA sessions were conducted from 2020 to 2022 covering adrenal, metabolic bone, thyroid, diabetes, and reproductive endocrinology. Medical students in year 1 and year 2 medical and year 3 pharmacy students were invited to participate in the session. Cases used for SGT were converted to SIMBA transcripts. These transcripts were reviewed and approved by clinicians and teachers involved in SGT with a focus on curriculum learning objectives and equivalence between SIMBA and SGT transcripts. On the day of the simulation, participants solved three interactive clinical cases during each session, followed by a Q& A session with an expert to resolve any queries participants had during the simulation. All students were invited to complete a survey following SIMBA which included 12-15 multiple-choice questions (MCQs) depending on the session. All SGT participants were also invited to complete the same survey. This resulted in three groups- those who attended SIMBA only, SGT only and those who attended both SIMBA and SGT. Median MCQ results as percentages were compared between groups using Wilcoxon signed rank test. The answers to Likert

scale questions were expressed as percentages. Open-ended questions from surveys underwent content analysis.
Results
130 students attended 15 SIMBA sessions during the study. The median MCQ result was significantly higher in the SIMBA-only group than in the SGT-only group ($P < .0001$). A large proportion of students agreed that SIMBA was easy to follow (91%), engaging and interactive (82%), stimulated their interest in endocrinology (82%), promoted new knowledge (90%), and provided an in-depth understanding of the topic (94%). 89% enjoyed the session overall and 83% would like to have SIMBA alongside SGT. Content analysis revealed themes of knowledge application through case-based learning, a deeper understanding of the topic, and instantaneous feedback.
Conclusions
SIMBA is a good alternative model for SGT to teach endocrinology to pre-clinical medical and pharmacy students by providing engaging, interactive, and interesting sessions. A future study focusing on cost-effectiveness analysis between the two models is underway to identify if SIMBA can replace SGT or be delivered in addition to SGT.

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P608

Intestinimonas butyriciproducens improves glucose metabolism in subjects with obesity and prediabetes: preliminary data from a randomized controlled trial

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As the prevalence of type 2 Diabetes Mellitus (T2D) is constantly increasing and the current prevention is not enough, new effective strategies are necessary, in particular in high-risk individuals. Therapeutic microbiology is one of further proposed targets, and, in particular, butyrate-producing bacteria can improve metabolic parameters in obese patients. Our study aims to evaluate the effect of *Intestinimonas butyriciproducens* as a preventive therapy for T2D in prediabetes, since it is able to decrease Advanced Glycation End Products (AGEs), convert sugars and proteins in butyrate, and increase insulin sensitivity. The trial is a double-blind, randomized, placebo-controlled (phase 1) and open label pilot study with two different doses (phase 2). *I. butyriciproducens* (10^5 CFU/day) or placebo were given for 12 weeks, then subjects in placebo will start the treatment (10^5 CFU/day), while the other group will increase the dose (10^8 CFU/day) for 14 weeks. We included overweight/obese patients with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Patients were assessed for clinical, biochemical and microbiota parameters at the time of recruitment (V1), after 12 weeks (V7) and 26 weeks of treatment (V10), during which the eating and lifestyle habits were also evaluated. Fourteen out of the 26 patients programmed, have been closed phase 1 and/or 2. In the first 7 patients who completed the study, those who have taken the probiotic since the beginning of the study had a significant improvement in the fasting and post-OGTT glucose-insulin metabolism. In particular, HOMA-index decreased over time in treated patients (V1: 3.3 $\pm$ 1.3; V7: 2.6 $\pm$ 1.5, V10: 2.5 $\pm$ 1.3), whereas remained about unchanged in placebo group (V1: 3.2 $\pm$ 1.1, V7: 3.5 $\pm$ 1.0, V10: 3.4 $\pm$ 1.3). Flash glucose monitoring data were stable. These findings were confirmed in the other 7 patients who completed phase 1. Serum AGE concentrations showed a trend towards a decrease in treated patients. Microbiota analyses are ongoing. In conclusion, *Intestinimonas butyriciproducens* seems to improve insulin resistance and inflammation in patients treated for a longer period, likely due to the time or dose. Since the study is still ongoing, the data should be confirmed. *Intestinimonas butyriciproducens* could be a new strategy in the work-up of T2D prevention.

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Comparing performance of healthcare professionals from different training grades in SIMBA simulation-based training sessions

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Introduction
Simulation via Instant Messaging – Birmingham Advance (SIMBA) is a simulation-based training model shown to have increased clinicians' confidence in managing cases in diabetes and endocrinology, as well as sustained clinical knowledge.[1] Traditional simulation models have typically focussed on a specific group of healthcare professionals. We evaluated if there is a difference in performance between different training groups during SIMBA.
Methods
All participants who completed both pre-and post-SIMBA surveys in 17 SIMBA sessions between May 2020 and June 2022 were included in this study. Participants' performance was assessed using the Global Rating Scale (GRS), which was adapted for each session and scored the participant on a scale of 1 (poor) to 5 (excellent) in 6 domains: History Taking, Physical Examination, Investigations, Result Interpretation, Clinical Judgement, and Management. Participants were grouped as junior grade (foundation year trainees, internal medical trainees and equivalent), middle grade (specialty training years 3 to 7 and equivalent) and senior grade (consultants and equivalent). Adjusted means and 95% confidence intervals of the scores for the six GRS domains were calculated using multiple linear regression models, adjusting for sex, country, training, and number of WhatsApp messages. The mean difference of the pairwise comparisons between each of the performance scores was calculated using a paired t-test.
Results
A total of 207 (junior grade – 59 (28.5%), middle grade – 116 (56.0%), and senior grade – 32 (15.4%)) from 49 countries were included in this analysis. Except for history taking where junior grade participants scored higher than the other two groups (junior vs middle vs senior: 4.2 vs 3.7 vs 3.7; $P = .0055$), there were no significant differences between the three groups on other GRS domains (Physical Examination (4.0 vs 3.7 vs 3.4; $P = .0688$), Clinical Interpretation (2.6 vs 2.6 vs 3.0; $P = .244$), Investigation (3.5 vs 3.4 vs 3.6; $P = .5573$)), Clinical Judgement (3.4 vs 3.3 vs 3.4; $P = .7891$), Management (2.8 vs 2.7 vs 2.7; $P = .8459$).
Conclusions
SIMBA provides equivalent simulation-based learning experiences irrespective of training grade. Combining these results with our previously published data on sustained improvement in clinical knowledge makes SIMBA an effective medium of teaching and learning for endocrinology.
References
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A Case Report: Rapidly Onset Fournier'S Gangrene In Empagliflozin Treatment for Type 2 Diabetes

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Introduction
Sodium/glucose co-transporter 2 (SGLT2) inhibitors are a relatively new group of antihyperglycaemic medications for type 2 diabetes mellitus (T2DM). Euglycemic diabetic ketoacidosis (EDKA) and Fournier's gangrene (FG) are uncommon advers effects of SGLT2 inhibitors. We report a case of a 52-year-old man who developed FG and EDKA after starting the SGLT2 inhibitor empagliflozin.
Case Presentation
A-52 years old male patient attended to the emergency department with bilateral red-swollen perineal lesion of one day evolution. Patient had a history of T2DM

under poor glycemic control for 10 years. He was using glyclazide 30 mg/d. He started to use empagliflozin treatment for his high HbA1c levels (12.2 %) two days before the development of the lesion. In suspicion of FG, pelvic CT scan was taken and severe subcutaneous air was reported in the lesion consistent with FG. Emergent surgical debridement was performed and after surgery he was followed in surgical ICU. During follow-up, the patient became tachypneic, lethargic and he had no response to verbal stimulus. The patient had severe acidosis, low bicarbonate level and euglycemia (pH:6.90, bicarbonate 4.9 mEq/l, lactate:1.7 mmol/l, plasma glucose: 189 mg/dl). After diagnosis of EDKA, continuous intravenous regular insulin and saline infusion was started. After 20 h of treatment, patient's plasma pH level increased to 7.26 and bicarbonate level increased to 19.9 mEq/l. His state of counciousness improved and GCS scored 15. The patient is still under intensive insuline therapy, antibiotherapy and negative pressure dressing for FG.

Conclusions

FG is a necrotizing infection of the tissue under the skin of the perineum. The incidence is 1.6 cases per 100×000 population. Poorly controlled diabetes, obesity, chronic alcoholism and immunosuppression are risk factors for FG. The duration of FG development after the use of SGLT2 inhibitors varies between 10 days and 6 years in the literature. In our patient, FG developed in a very short time, 2 days after starting SGLT2 inhibitor. EDKA is a clinical feature in which blood sugar is within normal limits, accompanied by acidosis and ketosis. In the perioperative setting, typical signs and symptoms of EDKA can confound the diagnosis and mistakenly be attributed to clinical presentations during the postsurgical state. EDKA, should be considered in the differential diagnosis and treatment should be started without delay. It is imperative that clinicians evaluate the benefits and risks associated with SGLT-2 inhibitors in diabetic patients at high risk of FG who do not use insulin.

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P611

Gaucher Disease Type 3c: A Rare Metabolic Disease Diagnosed In Adulthood

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Background

Gaucher disease (GD) is the most prevalent lysosomal disorder caused by *GBA* mutations and abnormal glucocerebrosidase function, leading to glucocerebroside accumulation mainly in the liver, spleen, bone marrow, lungs, and occasionally in the central nervous system. Gaucher disease type 3c (GD3c) is a rare subtype of the subacute/chronic neuronopathic GD3, caused by homozygosity for the *GBA* p. Asp448His (D409H) mutation.

Case Report

A 24-year-old male patient. He first applied to neurology with the complaint of spasms in the hands and neck. In the evaluation, hepatosplenomegaly and mild pancytopenia were detected. His cytopenia, eye and neurological findings have been present since early childhood. In the family history, his father died at the age of 35 and his brother at the age of 19 due to cardiac reasons. On physical examination, the patient's vertical eye movements were limited and bradykinesia was detected. In addition, the patient had brown macules scattered on his trunk, diagnosed as tinea versicolor. Bilateral hallux valgus was detected in the orthopedic evaluation. In the complete blood count, the white blood cell count was $3.39x10^9$/l(4.5-11), the hemoglobin level was 8 g/dl(13.2-17.3), and the platelet count was $35x10^9$/l(150-400). In addition, his transferrin saturation was 25%(13-45), total iron binding capacity was 302 mg/dl (250-450), serum iron level was 77 mg/dl(37-145), ferritin level was 987ng/ml(30-400), B12 level was 216 pg/ml(197-771), HDL cholesterol level was 27 mg/dl(40-60). In the MRI volumetric evaluation, the liver volume was 1300cc and the spleen volume was 9959cc. The patient has had no complain of chest pain or exertional dyspnea. In the echocardiographic examination, the aortic and mitral valves were thick. Aortic valve opening was found to be slightly restricted. On MRI of bones, heterogeneous bone marrow intensity was detected in both femur and pelvic bones, there was no osteonecrosis. In bone mineral densitometry, the femoral neck Z score was- 0.2 and the lumbar total Z score was -2.2. Orbital and cranial MRI revealed hydrocephaly, partial empty sella, hyperintense signal foci in T2AG and FLAIR sequences in periventricular and subcortical areas, and thickening in the calvarium. In the psychiatric evaluation, no pathological findings were detected, except for the anxiety. Genetic examination was performed with the preliminary diagnosis of GD. NM-000157.4 c.1342G>C(p.Asp448His) homozygous mutation was detected in the GBA gene compatible with the diagnosis of Gaucher disease type 3c. Thereupon, the patient was started with enzyme replacement treatment as velagluceridase alfa at a dose of 60 U/kg once every 15 days.

Conclusions

Although clinic presentation is variable, heart valve diseases, aortic calcification, oculomator apraxia, abnormal eye movements, corneal opacities, pancytopenia, hepatosplenomegaly, hydrocephalus are the main findings of GD3c.GD3c should definitely be considered in patients with these findings.

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Obesity-Associated Hepatic Steatosis, Somatotropic Axis Impairment and Ferritin Levels are Strong Predictors of COVID–19 Severity

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Purpose

From a clinical perspective, the full spectrum of Sars–CoV–2–infected patients has not yet been defined. This study aimed to evaluate whether liver density on computed tomography (CT) scan and serum insulin-like growth factor 1 (IGF1) values can explain the clinical variability of COVID–19 cases.

Methods

We performed a retrospective study including SARS–CoV–2–infected patients hospitalized from March 2020 to May 2021 at Umberto I Polyclinic of Rome. Patients were divided into four groups (0–mild, 1–moderate, 2–severe, and 3–critical) according to respiratory failure. Routine laboratory examinations, BMI, liver steatosis indices, CT quantification of hepatic attenuation, and IGF1 serum levels have been assessed and correlated with COVID–19 severity. Hepatic attenuation was defined as the mean density of three regions of interest expressed in Hounsfield (HU).

Results

Mean liver density was 50.7 ± 9.5 HU, whereas mean GH and IGF1 were 0.92 ± 1.06 ng/ml and 97.2 ± 63.4 ng/ml, respectively. Analysis of variance between groups showed that patients with worse prognoses had higher BMI, lower liver density, and significantly lower concentrations of albumin, GH, and IGF–1. ROC analysis confirmed the prognostic accuracy of serum IGF1 in discriminating patients with the occurrence of death/severe respiratory failure. (AUC 0.688, CI: 0.587 to 0.789, $P < 0.001$). A multivariate analysis considering the degrees of severity of the disease as the dependent variable and ferritin, liver density, and the standard deviation score of IGF1 as regressors showed that all three parameters were significant predictors ($B = 0.37$, $P < 0.001$; $B = -0.36$, $P < 0.001$ and $B = -0.21$, $P = 0.03$ respectively).

Conclusions

IGF-1 and liver steatosis account for the increased risk of poor prognosis in COVID-19 patients with obesity.

Keywords

Liver steatosis; liver density; obesity; SARS-CoV-2 infection; COVID-19; ferritin; growth hormone; IGF1

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Long-term Body Composition in Patients With POMC or LEPR Deficiency Obesity Following Setmelanotide

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Objective
Ideally, treatment strategies designed to reduce weight or body mass index in patients with obesity should reduce fat mass while preserving lean mass because reduced lean mass can negatively impact overall health and energy expenditure, thus favoring weight regain. In Phase 3 trials, 1 year of treatment with the melanocortin-4 receptor agonist setmelanotide led to weight reduction in patients with obesity due to biallelic variants in the genes encoding proopiomelanocortin (POMC)/proprotein convertase subtilisin/kexin type 1 (PCSK1; mean −25.6% change from baseline) or leptin receptor (LEPR; mean −12.5% change). The current analysis assesses changes in total fat and lean mass over 2 years in adult and pediatric patients who achieved beneficial weight loss at 1 year of treatment.
Methods
Patients with POMC, including PCSK1, or LEPR deficiency aged ≥6 years who demonstrated clinical benefit and acceptable safety after treatment with setmelanotide in a prior (index) trial continued treatment in a long-term extension trial (NCT03651765). Body weight measures and safety were assessed. Body composition was measured by dual-energy x-ray absorptiometry and reported as percent change in total fat and lean mass from index trial baseline in patients who achieved ≥10% weight reduction (≥18 years old) or ≥0.3-point body mass index Z score reduction (<18 years old) after 1 year of treatment.
Results
Across all patients ($n=24$), mean (standard deviation [SD]) percent changes in total fat mass were −37.2% (13.0%; $n=22$) at Month 12 and −32.4% (16.7%; $n=17$) at Month 24. Smaller mean (SD) percent changes were seen in lean mass at Month 12 (−7.8% [10.8%]) and 24 (−6.5% [16.2%]). No new safety issues were observed during long-term treatment.
Conclusions
Setmelanotide demonstrated clinical benefit in total fat mass reduction while achieving a relative maintenance of lean mass over 2 years of treatment.

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Serum Vitamin B12 Levels and Diabetic Retinopathy in Type 2 Diabetes

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Introduction
Diabetic retinopathy (DR) is a serious microvascular complication of type 2 diabetes and the leading cause of blindness worldwide. Several studies have reported the association between metformine-induced vitamin B12 deficiency in type 2 diabetic patients. However, the association between vitamin B12 and DR has only been investigated in few studies.
Materials and methods
A cross-sectional study was carried out on 123 type 2 diabetic patients treated with metformin. One hundred and four patients had a fundus examination: sixty eight patients with DR, 36 patients without DR. Vitamin B12 levels were measured in all participants.
Results
The mean age of the subjects (DR+) was 61.34±6.62 years vs 60.61±6.79 years in patients (DR-). In the patients (DR+) 30.9% were male vs 33.3% (DR). The mean duration of diabetes was 17.72 ±4.1 years in (DR+) and 13.92 ±7.57 years in (DR-) with a significant difference ($P=0.01$). The mean FBG was 12.53 ± 4.53 mmol/l and 10.58 mmol/l ± 4.53 mmol/l respectively with significant difference ($P=0.039$). However, there was no difference in mean HbA1c between the 2 groups. Blood levels of vitamin B12 were comparable between patients (DR+) (360.76 ± 165.12) and (DR-) (350.26 ± 219.20). There was no correlation between cobalamin levels and retinopathy ($P=0.78$). Mean metformin dose was 1908.82 ±606.79 in patients (DR+) and 1984.72±538.36 in patients (DR-). There was no correlation between metformin dose and DR $P=0.5$. The mean folate level was 7.82±3.19 in patients (RD+) and 8.41±4.25 in patients (DR-). There was no correlation between folate levels and retinopathy.
Conclusion
This study shows that vitamin B12 deficiency does not seem to play a role in DR. Further studies are needed to assess the real impact of vitamin B12 deficiency on DR and to evaluate the Impact of supplementation.

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P615

Association between diabetic peripheral neuropathy (DPN) and Hypertiglyceridemia in patients with type 2 diabetes in Georgia

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Background
Diabetic neuropathy is the most prevalent chronic complications of diabetes. This heterogeneous group of conditions affects different parts of the nervous system and presents with diverse clinical manifestations. Diabetic peripheral neuropathy (DPN) is one of the common complication of type 2 diabetes and can lead to foot ulcer, gangrene or amputation. The risk of developing diabetic neuropathy increases with age, diabetes duration and poor control of blood glucose. About 60% to 70% of all people with diabetes will eventually develop DPN. Hypertiglyceridemia is a typical lipid disorder in patients with poorly controlled diabetes mellitus.
The Aim
Of this study was to assess the effect of hypertiglyceridemia on peripheral neuropathy in patient with type 2 diabetes(T2DM).
Methods
62 T2DM patients with peripheral neuropathy were enrolled in this study; among them, 33 men and 29 women (Study Group/SG). Their mean age was 56±7 yrs and diabetes duration varied from 5 to10 yrs. In all SG patients hypertiglyceridemia was diagnosed. 50 patients with the same age, sex and diabetes duration, but without DPN and normal triglycerides (TG) were used as controls (CG). HbA1c in SG was 8,1±1,2% and in CG - 7,7±1,1%. According to current Guidelines, to assess DPN, following neuropathy tests were performed in all patients: 10-g monofilament test, tip-term/temperature test, vibration test with the 128-Hz tuning fork, pick tests and neurological examination with Sudoscan. Results of all neurological tests in SG patients (monofilament test, tip-term/temperature test, vibration test) were positive, Sudoscan examination revealed presence of small fiber neuropathy. In CG patients all tests, except Sudoscan, were negative, while Sudoscan revealed small fiber damage. Association between hypertiglyceridemia and DPN was assessed. Serum triglyceride levels in SG patients were elevated(mean TG level 299± 45mg/dl, while in CG patients - 100±20mg/dl).
Results
According to neurological examinations prevalence of DPN in SG patients comprised 64,5% (40 cases). TG concentration was significantly elevated in T2DM patients with DPN when compared to patients without DPN and normal TG levels($P=0,005$). Elevated serum triglyceride levels were associated with DPN($P<0,044$).
Discussion
This study shows that increased levels of serum triglycerides may play important clinical role in development of DPN in T2DM patients in Georgia. The problem needs further investigation with other important parameters.

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P616

Gender differences in lower limb amputations among persons with diabetes

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Background and Aim
Recent international studies indicate a secular decrease in the proportion of patients with diabetes who undergo lower limb amputations (LLA). However, our findings suggest that the proportion of diabetics among patients undergoing non-traumatic, non-cancer related lower limb amputations has increased over the past decades despite comprehensive preoperative investigations and other surgical interventions. To further explore the underlying reasons for this, we aimed to explore any gender differences in the preoperative treatment and assessment regarding indication for vascular surgery.
Methodes
Medical records for all patients identified with LLA by the electronic discharge registers at Innlandet Hospital, Elverum, from 2013 through 2019 were retrieved. Traumatic and cancer-related amputations were excluded. All codes for amputations and exarticulations were included, and amputations were verified by manual review by two of the authors. Only the first minor or major amputation in an individual were included in further analyses. Diabetes was defined by the

WHO criteria. Descriptive statistics and chi-square tests were performed using the SSPS TM version 26
Results
We identified 190 persons undergoing non-traumatic, non-cancer related amputations of the lower limb. Of the 120 men 70 % had type 1 or 2 diabetes. 50% of the women had diabetes. 66 % of the persons with diabetes and 72 % of the persons without diabetes had a vascular angiography (CT, MRI or conventional) preoperative. The proportion of amputees who underwent an angiography of the lower limbs were higher in men than in women ($P=0.048$). When stratifying in groups with and without diabetes, this difference was found only in the non-diabetes group ($P=0.004$). No statistical differences were found regarding other markers or risk factors of vascular disease, such as smoking, use of statins or anti-platelet agents.
Conclusion
The gender difference in favour more investigations with preoperative angiography before LLA in men, was not found in persons with diabetes, indicating equal treatment across the genders in this group.

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P617

Case Report: Atypical presentation of central pontine myelinolysis in hyperglycemia

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Central pontine myelinolysis (CPM) is a neurological disorder typically caused by rapid correction of severe chronic hyponatremia. Conditions causing a hyperosmolar state can also cause CPM, but it is rarely seen in diabetes. We report the case of a 33-year-old woman with personal history of Type 1 Diabetes since she was 9 years old with very poor metabolic control (A1hbC 15%) and microvascular complications, who attended the emergency department due to left hemicranial headache for the past 2 days that subsided with the analgesia prescribed in the emergency room. As an incidence laboratory result showed a glycemia of 676mg/dl without ketoacidosis, increased serum osmolality, and normal sodium, so insulin therapy was started in the emergency room and she was discharged the next day asymptomatic with a glycemia of 183mg/dl. She went back to the emergency room 24 h later due to language impairment with difficulty in issuing words. MRI brain demonstrated a symmetric lesion in the central pons with increased signal intensity on T2- and diffusion-weighted images. After neurological consultation and MRI confirmation, the patient was diagnosed with CPM secondary to hyperosmolar hyperglycemia. Twelve-week-follow up with neurology was notable for near-complete resolution of symptoms and MRI alterations. The patient is currently undergoing Endocrinology check-ups with good metabolic control (A1HbC 6.7%) This is a case report of central pontine myelinolysis (CPM) associated with hyperglycemia, which is unique in several aspects: CPM occurred in the setting of uncontrolled hyperglycemia with normal corrected serum sodium and no other electrolyte abnormalities. The presentation was atypical with intermittent symptoms and patient remained alert without corticospinal involvement. Despite the pronounced fluctuations in serum osmolality, central pontine myelinolysis (CPM) is rarely seen in diabetics. This case report of CPM associated with hyperglycemia highlights the importance of adequate blood glucose control in diabetics. CPM can present atypically in diabetics and is only diagnosed in the presence of a high index of clinical suspicion.

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Oxidative Stress and Biochemical Indicators In T2DM

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Introduction
Many complications of T2DM, including retinopathy and renal failure, have been associated with glucose and triglyceride metabolism. Hyperglycemia causes oxidative stress mainly due to the enhanced production of mitochondrial reactive oxygen species ROS, non-enzymatic protein glycosylation and glucose autoxidation. Elevated levels of free fatty acids can contribute to oxidative stress by promoting mitochondrial oxidation. Furthermore, oxidative stress caused by hyperglycemia and free fatty acids leads to the activation of stress-sensitive signaling pathways, which impair both insulin secretion and action and promote the development of T2DM.
Aim
The aim of this study is to determine the possible correlation of glucose Glu, cholesterol Chol, HDL-Chol, LDL-Chol, triglycerides TG, plasma uric acid UA and glycosylated hemoglobin HbA1c with the levels of oxidized lipids in plasma and in red blood cells, diabetics and normal patients.
Materials and Methods
The study included 30 T2DM volunteers with plasma Glu levels $>$ 125mg% and HbA1c $>$ 7.0% and 30 normal volunteers who were the control group. Oxidative damage was determined by the thiobarbituric acid TBA method. The assay photometrically measures the malondialdehyde MDA contained in the sample as well as the MDA generated by lipid hydroperoxidases under the hydrolytic reaction conditions. Glu, HDL-Chol, LDL-Chol, TG, UA and HbA1c determinations were performed on a biochemical analyzer.
Results
In the control group, Glu levels were 84 ± 8 mg%, TG 78 ± 28 mg%, HDL 57 ± 8 mg%, LDL 115 ± 27 mg%, UA 5.6 ± 1.5 mg%, HbA1c 5.4 ± 0.2%, plasma TBA 0.023 ± 0.013 μmol/l and hemolysate TBA 0.017 ± 0.005 μmol/l. In the diabetic patient group, Glu levels were 152 ± 25mg%, TG 185 ± 50mg%, HDL 40 ± 10mg%, LDL 100 ± 40mg%, UA 6.1 ± 1.5mg%, HbA1c 7.8 ± 0.2%, plasma TBA 0.112 ± 0.043μmol/l and blood plasma TBA 0.015 ± 0.005μmol/l. TBA levels in the control group were statistically significantly lower than those in the diabetic group. In the group of diabetic patients, a positive correlation was found with Glu -HbA1c ($r=0.889$, P-value <0.001), LDL–Chol ($r=0.686$, P-value $=0.01$), LDL–HDL ($r=0.649$, P-value $=0.016$), TG–Glu($r=0.548$, P-value $=0.042$), plasma TBA–HbA1c($r=0.549$, P-value $=0.023$), plasma TBA-Glu ($r=0.593$, P-value <0.001) and negative correlation HDL-TG ($r=-0.684$, P-value $=0.01$), LDL-TG ($r=-0.72$, P-value $=0.006$). In the control group, a positive correlation was found between LDL – Chol ($r=0.964$, P-value <0.001) and plasma TBA-TG ($r=0.773$, P-value $=0.009$).
Conclusions
The present study in the Greek population showed increased TBA levels in the T2DM group and a positive correlation with Glu and HbA1c levels. Further correlation with other markers would complete the study.

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P619

Pancreatic autoimmunity in the diagnosis of type 1 diabetes: usefulness of zinc transporter 8 and proposal for stepwise assessment

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Introduction
Zinc transporter 8 (ZnT8) autoimmunity has been established as one of the markers for the diagnosis of type 1 diabetes (T1D) along with glutamate decarboxylase (GAD) and tyrosine phosphatase IA-2 (IA-2) antibodies. The aim of this study is to understand the status of pancreatic autoimmunity in the diagnosis of T1D, with special attention to the usefulness of ZnT8. In addition, as a second objective, we study the proposal to perform the assessment of pancreatic autoimmunity using a stepwise approach.
Methods
We studied all ZnT8 tests performed in Asturias (Spain) since the introduction of ZnT8 analysis in April 2017 until December 2020 and how many of the 304 new diagnoses of T1D in this period had ZnT8, GAD or IA2 as the only positive antibody. Autoinmunity was considered positive if GAD>10, IA2>10 and ZnT8>20 units/ml. Finally, the proposed stepwise assessment is determined with initial analysis of GAD, subsequent study of IA2 if GAD negative and final evaluation of ZnT8 if the previous two were negative.
Results
Since the introduction of ZnT8 in our laboratory, 2388 studies have been performed in a total of 2096 patients, with a duplication in 188 patients. Of these

2096 patients, 266 patients (12.69%) had anti-ZnT8. Of these, 146 were new diagnosis of T1D in this period. In the 304 patients diagnosed with T1D included, the prevalence of anti-GAD was 74.01%, anti-IA2 45.07% and anti-ZnT8 48.03%. Of these patients, 5.59% had ZnT8 as the only positive antibody, while in the case of GAD and IA2 it was 31.58% and 6.91%, respectively. Regarding the stepwise study proposal, of the 304 patients diagnosed with T1D, 225 had anti-GAD and therefore no IA-2 or ZnT8 study would be performed in them. Of the remaining 79 patients, 45 were positive for IA2 and would not need to be tested for ZnT8. Therefore, if the analysis would have been performed in a staggered manner, 74.01% of the IA2 and 88.82% of the ZnT8 studies would have been avoided.

Conclusions

The frequency of GAD is higher than IA2 and ZnT8 and may serve as the first antibody to be requested in case of suspected T1D. ZnT8 is useful in a limited number of patients so measures should be sought to increase the effectiveness of the technique. The assessment of pancreatic autoimmunity in a stepwise manner may be a useful strategy to reduce unnecessary testing and consequently reduce healthcare costs.

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P620

Mutation in MT-TV gene – a novel etiology of mitochondrial diabetes?

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Mitochondrial diseases are rare conditions with a wide phenotypic range. The inability of dysfunctional mitochondria to produce sufficient ATP results in multi-organic defects dependent on high aerobic such as pancreas. The most common endocrine disease related to mitochondrial diseases is diabetes *mellitus* and it is thought to be secondary to insulin deficiency. A 26-year-old pregnant patient with 26 weeks gestational age was referred to an Endocrinology appointment due to diagnosis of diabetes *de novo* in pregnancy (oral glucose tolerance test - OGTT: fasting plasma glucose 187 mg/dl; 2-hour plasma glucose 417 mg/dl). The patient had no relevant past medical history or diabetes history in family and her regular medication were pregnancy vitamins. She denied catabolic symptoms. The actual HbA1C was 7.3% and pancreatic autoantibodies were negative. Before pregnancy, body index mass was normal. She was started on basal-bolus insulin therapy (insulin detemir 8 units plus insulin aspart 2+2+2). During medical follow-up, insulin aspart was suspended due to overall good postprandial glucose levels and basal insulin was maintained. Two weeks later the patient had a preterm delivery (36 weeks and 6 days); birth weight was 2.25 kilograms (4.94 lb). By this time, she discontinued insulin therapy and was started on metformin 700 mg b.i.d. and a genetic panel was conducted. It was identified a m.1644G>A variant in Mitochondrially Encoded tRNA Valine gene (MT-TV) with 82% heteroplasmy. This gene encodes transfer RNA that attaches specifically to valine ($tRNA^{Val}$) and therefore assists in protein synthesis involved in oxidative phosphorylation. *ClinVar* and *Mitomap* databases consider this variant as probably pathogenic and it has been associated to Leighs' syndrome, hypertrophic cardiomyopathy and mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS). Nevertheless, it has never been reported as a diabetes causative gene. Since this variant may reduce the amount of $tRNA^{Val}$ available and impair mitochondrial function, the authors speculate if this mutation may be associated with diabetes surge.

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P621

Asymptomatic Pyuria/Bacteriuria and Urinary Tract Infection Risk in Women Initiated SGLT2 Inhibitors

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Objective

The study aims to investigate the association between asymptomatic pyuria/bacteriuria at the initiation of SGLT2 inhibitors (SGLT2i) and urinary tract infection (UTI) risk in a cohort of women with type 2 diabetes mellitus (T2DM) (NCT05520684).

Methods

The female outpatients with T2DM under follow-up in the department of internal medicine and initiated SGLT2i (dapagliflozin/empagliflozin) were included between February and September 2022. Exclusion criteria were; being symptomatic for UTI or genital infection at the initiation, being treated for UTI or genital infection in the past 3 months or having a high risk for UTI (any urological disease/catheter use, cancer, immunodeficiency, bedridden). Hospitalization and antibiotic use for indications other than UTI were exclusion criteria during follow-up. Automated urinalysis and urine culture were obtained on the SGLT2i initiation day. Pyuria was defined as ≥ 3 white cells per high-power field. Any bacterial growth in the culture reported by the microbiology laboratory was defined as bacteriuria. All patients were followed up for 3 months after SGLT2i initiation. UTI diagnosed or treated by any physician was recorded as the outcome. Cumulative incidence and relative risk of UTI were analyzed for pyuria and bacteriuria.

Results

143 female patients were included. 13 patients were excluded during follow-up (antibiotic use $n=7$, hospitalization for CABG $n=1$, DHF $n=1$, NSTEMI $n=1$, CVA $n=1$, acute pancreatitis $n=1$, PTE $n=1$). The median age was 62 (range 34-87). 20.8% of the patients ($n=27$) had cardiovascular disease. Median HbA1c was 9.1%(range 5.9-13.9). Median creatinine and eGFR were 0.79 mg/dl (range 0.4-1.77) and 80 ml/min (range 32-120), respectively. 41.5% of the patients ($n=54$) had pyuria and 28.5% ($n=37$) had bacterial growth in urine culture. The most common microorganisms were E. coli ($n=13$, 35%) and S. agalactiae ($n=7$, 19%). Dapagliflozin was initiated in 70% of patients ($n=91$). The cumulative incidence of the UTI was 20%($n=26/130$) in the whole cohort, 25,9% ($n=14/54$) in the pyuria group and 18.9% ($n=7/37$) in the bacteriuria group. The relative risk of UTI was 1.64 (95% CI: 0.82-3.26) for pyuria, 0.92 (95% CI: 0.42-2.01) for bacteriuria and 1.2 (95% CI: 0.47-3.08) for pyuria plus bacteriuria. Multiple logistic regression analysis including the variables of age, HbA1c, CVD as comorbidity, eGFR, pyuria, bacteriuria and SGLT2i type did not reveal any statistical significance.

Conclusions

In this pragmatic practical cohort study, pyuria or bacteriuria at the initiation of SGLT2 inhibitor are not risk factors for UTI for female patients with type 2 DM in a 3-month-follow-up.

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P622

Hybrid Closed Loop in obesity: to each his own (algorithm)!

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Introduction

Currently, patients with type 1 diabetes (T1D) have the option of being treated with Hybrid Closed Loop (AHCL) systems, which allow insulin delivery to be modulated according to glycemic values. These systems do not allow any kind of anthropometric or laboratory characteristics to be used to enhance the devices' capabilities. Thus, the aim of our study was to investigate the efficacy of AHCL systems in subjects with T1D and with obesity compared to normal-weight subjects in terms of metabolic control.

Methods

Forty-one subjects with T1D and normal weight (BMI 18.8-24.9 Kg/m^2) or obesity (BMI 30.3-36.6 Kg/m^2) were treated with AHCL and were enrolled in this retrospective observational study. BMI, fasting plasma glucose, Hba1c, lipid profile, creatinine, Time In Range 70-180mg/dl (TIR), Time above range with glycemia 180-250mg/dl ($TAR^{180-250}$), Time above range >250mg/dl ($TAR^{>250}$), Time Below range with glycemia 70-54mg/dl (TBR^{70-54}), Time Below range <70mg/dl ($TBR^{<54}$) and glycemic variability were assessed.

Results

We enrolled 41 subjects (13M/28F; age:47 $\pm$ 12 years; BMI: 26.7 $\pm$ 4.9 kg/m2; mean duration of T1D: 26 $\pm$ 12 years). Hba1c (8.6 $\pm$ 2% vs 7.4 $\pm$ 0.8 %, $P=0.021$) and TG (122 $\pm$ 70mg/dl vs 73 $\pm$ 29mg/dl, $P=0.012$) were shown to be significantly higher in patients with obesity when compared to normal weight subjects while there were no differences in terms of fasting plasma glucose, total cholesterol, HDL, LDL and creatinine. AHCL prediction algorithms showed different efficacy in patients with obesity when compared with normal weight patients: although the TIR (mean 63.1 $\pm$ 16.4), $TAR^{>250}$ (mean 9.2 $\pm$ 10.5) and both TBR^{70-54} (mean 1.1 $\pm$ 1.1) and $TBR^{<54}$ (mean 0,4 $\pm$ 1) did not show statistically significant differences, patients with obesity when compared to normal weight patient showed higher $TAR^{180-250}$ (23.9 $\pm$ 8.3% vs 34.3 $\pm$ 10.1%,

$P=0.003$) and higher prevalence of high (>36%) glycemic variability (33.3% vs 66.7% $P=0.05$).
Conclusions
T1D subjects with obesity had worse glycemic control, evidenced not only by laboratoristic parameters such as higher levels of Hba1c and triglycerides but also by the higher TAR $^{180-250}$ and greater presence of patients with high glycemic variability when compared with normal weight. This suggests that AHCL algorithms should also take into account the anthropometric characteristics of the subjects in order to better tailor insulin treatment.

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P623

Hirata disease: a rare cause of hypoglycemia

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Introduction
Hirata disease (or Insulin autoimmune syndrome) is characterized by the presence of high concentrations of insulin autoantibodies leading to hyperinsulinemic hypoglycemia in individuals with no history of prior exposure to exogenous insulin. Etiopathogenesis is not completely elucidated, it's considered to result from the interaction of genetic predisposition and environmental triggers such as: medications (methimazole, carbimazole, alpha-lipoic acid, captopril, diltiazem, clopidogrel, diclofenac, pantoprazole, omeprazole), viral infections (mumps, rubella, varicella zoster, hepatitis C virus), and hematological disorders (multiple myeloma, monoclonal gammopathy).
Case report
A 67-year-old female was referred to our clinic with frequent, daily episodes of unpredictable hypoglycemia (fasting, postprandial, and during physical activity) with autonomic and neuroglycopenic symptoms for about six months. Hypoglycemia (capillary blood glucose 42-55 mg/dl) was documented during these episodes with remission of symptoms and signs of hypoglycemia after glucose administration. She had a history of toxic multinodular goiter treated by surgery, prediabetes treated with lifestyle change, arterial hypertension, chronic ischemic heart disease, and old myocardial infarction. She was taking Indapamide, Amlodipine, Valsartan, Betaxolol, Clopidogrel and Pantoprazole. In addition, the patient did not previously use oral hypoglycemic drugs or exogenous insulin. Laboratory tests revealed normal thyroid and adrenal function, and normal chromogranin A (with prior interruption of Pantoprazole). We observed normal basal glucose level, HbA1c 6.99%, and very high insulin levels (19600 uU/ml). After 72-h fasting test, results revealed low glucose (55 mg/dl) with high insulin levels (8673 uU/ml), elevated C-peptide levels (9.44 ng/ml, NR: 0.8-3.85), high insulin/peptide-C molar ratio (>1), and high level of proinsulin (31 pmol/l, NR<11). Measurement of anti-insulin antibodies revealed high titers (>100 U/ml, NR<10). Abdominal CT scan showed no pancreatic or extra-pancreatic lesions. Regarding the presence of hypoglycemic hyperinsulinemia, high titers of insulin autoantibodies, and the use of medications associated with this disease, the diagnosis of insulin autoimmune syndrome was established. The treatment with Pantoprazole was stopped and Clopidogrel was switched to another drug, and the patient was advised to eat frequent and small meals with low carbohydrate content. After six months, our patient reported a decrease in the frequency of hypoglycemic episodes until complete remission.
Conclusions
Hirata disease is still an underdiagnosed condition with increasing incidence. Diagnosis of the disease is a challenge and differential diagnosis from other forms of hypoglycemia is mandatory to avoid unnecessary and high costs imaging examinations. In most cases is self-limited, but in severe cases, pharmacologic therapy is indicated.

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P624

Changes of Cholesterol and Cardiovascular Risk Before and After Initiation of Statin Therapy

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Introduction
Cholesterol management is essential to prevent coronary artery disease (CAD) and related complications. Lifestyle changes are first treatment, followed by statin therapy. Multiple studies have shown statins to effectively reduce the risk of cardiovascular complications. LDL cholesterol is the main measure to assess impact of statin therapy. However, CAD risk also depends on other often neglected risk factors. We present preliminary data of the evaluation of the simultaneous effect of statins on LDL cholesterol and CAD risk.
Methods
Retrospective cohort evaluation of Olmsted County residents (Minnesota, USA) seen at Mayo Clinic. Clinical data were collected searching electronic medical records. The cohort was divided based on statin treatment or not during the study period, and if they developed CAD or not 1 year after the index date. The index date (time=0) was the date of the first statin prescription, with follow-up of quarterly LDL levels and CAD risk scores (Framingham) between -10 and +10 years. An AI model to predict CAD and tailored to our population was used to validate the Framingham Risk score with similar results.
Results
Contrary to expectations, in the general sample the prediction model showed that LDL was a negative predictor (-0.0052) and statin a positive predictor (0.4670) of CAD. Subjects who developed CAD vs. those without CAD had lower LDL in the group without statins (mean 110.3 vs. 115.3 mg/dl) and in the group with statins (126.7 vs 135.2). Framingham risk score showed expected results, being higher in subjects who developed CAD vs. those without CAD, without statins (.079 vs .050) and with statins (.084 vs .067). Quarterly follow-up of those that received statin therapy, before and after the first statin prescription, showed a significant LDL reduction (approximately 30mg/dl) after statin initiation, being always higher in the group without CAD. However, the CAD risk showed no significant changes in either group at the time of statins initiation.
Conclusion
Our results support current practice of initiating statins based on calculated overall cardiovascular risk rather than LDL value alone. Despite a significant drop in LDL levels with statin therapy, the cardiovascular risk showed negligible changes, remaining higher in subjects who developed CAD. It is difficult to have a position on the statin mechanism impacting CAD based on the nature of our study. However, it seems evident that LDL reduction is insufficient, and better management of additional cardiovascular risk factors is critical and needed to prevent CAD complications.

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P625

Biomarkers of prostate cancer transgenerational transmission risk in the progeny of obese fathers subjected to dietary correction

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Metabolic disorders, such as overweight and obesity, are serious health societal challenges due to their high incidence rates. Obesity leads to metabolic dysregulation, promoting hormonal imbalance, oxidative stress, and a chronic inflammation state. Eating habits towards the intake of highly caloric fat-rich regimes induce epigenetic changes in the information transgenerationally transmitted. Furthermore, obesity promotes carcinogenesis. It is known that the prostate is sensitive to the metabolic and hormonal alterations promoted by obesity. Prostate Cancer (PCa) is the second most common cancer and the fifth leading cause of death among men. The diagnosis is generally based on the detection of PSA (prostate-specific antigen) and digital rectal examination. Further, PCa biomarkers, like homeobox Hox-B13 (HOXB13), are used for tissue diagnosis. Due to the close relationship between obesity and PCa development, as well as the emerging evidence on the inheritance of obesity-related factors, it has been debated if there are inheritable obesity-related changes that trigger

PCa. Still, to date, no data has been clearly reported showing the inheritance of obesity-related factors that could also promote the development of PCa. In this work, we studied the expression of HOXB13, a PCa biomarker, on the prostate of the progeny of fathers lean, obese, and subjected to diet correction after high-fat diet. To test this, a transgenerational animal model (*Mus musculus*) was established, where F0 mice were exposed to three different diets: standard, high-fat (HFD), and diet correction (60 days HFD, plus 120 days standard diet), *ad libitum* for 200 days post wearing. Two more generations were bred, F1 and F2, between males and lean females. We evaluated several PCa biomarkers expression on the prostates (Androgen receptor, HOXB13, Ki-67). Among these, HOXB13 presented a decreased expression on the prostates of F1 mice whose diet was corrected from HFD to standard. HOXB13 decreased expression is associated with carcinogenesis since it promotes lipid accumulation, which is a carcinogenesis hallmark. Obesity has already been correlated to altered DNA methylation patterns in several tissues, including the prostate. Concurrently, *HOXB13* promoter hypermethylation decreases *HOXB13* expression. These results suggest that the offspring of obese fathers subjected to diet correction have an increased risk of developing PCa. We propose that a diet correction from HFD to a standard diet may not be sufficient to revert the effects of HFD on DNA methylation and that this epigenetic alteration is being transmitted from the F0 to F1 animals as detected in *HOXB13* expression.

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P626

Comparison of the Effects of a Ketogenic Diet and an Isocaloric Balanced Diet administered to Obese patients on Quality of Life and Sleep: a Randomized Clinical Trial

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Introduction
The prevalence of obesity and metabolic disturbances is worryingly increasing worldwide, therefore the study of their pathophysiology is extremely important to find new strategies for their treatment. Obesity has an impact not only on the metabolism of the patients, but also profoundly influence their daily life, and potentially affect the quality of life and the quality of sleep. These latter are strictly related to the circadian rhythm of the individuals that, accordingly to animal models, can be influenced by the diet composition.
Aim
The aim of our research project is to study the effects of a ketogenic diet in comparison with an isocaloric balanced diet on quality of life and sleep quality in obese individuals.
Methods
24 obese patients referred to the CASCO centre (High Specialization Centre for the Care of Obesity) in Sapienza University, Umberto I Polyclinic, Rome, Italy, were enrolled and completed the study. The enrolled patients were randomly divided in 2 branches and prescribed a ketogenic diet or an isocaloric balanced diet (1200 Kcal per day, protein content 1.2-1.4 g/Kg of ideal body weight for each patient), for 30 days. Patients were encouraged to walk 30 minutes every day. Questionnaires for assessing quality of life and quality of sleep were administered at baseline and at the end of the study. In a subgroup of 20 patient, an actigraphy study for assessing sleep parameters was performed.
Results
Quality of life was significantly ameliorated after both diets, and ketogenic diet had a greater positive effect. We observed a reduction of daily sleepiness in both diets. The ketogenic diet was more effective in achieving better-quality sleep, but this may be related to the greater weight loss seen. Total sleep time was insufficient in both groups.
Conclusion
A hypocaloric balanced diet and an isocaloric ketogenic diet are both able to induce a significant amelioration of the quality of life of obese patients even in the short-term, and the ketogenic diet has a greater beneficial effect. Improved quality of life, and in particular of the physical function and self-esteem domains, may act as a motivating factor for adherence to the diet. Diurnal sleepiness was ameliorated after both diets, and sleep quality significantly improved after the ketogenic diet, which induced a greater weight loss. As good quality sleep is important for healthy metabolism, measures aimed to a better sleep hygiene should be encouraged as part of weight-loss programs.

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P627

Impact of Bariatric Surgery in Metabolic-Associated Fatty Liver Disease

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Introduction
In 2020, a group of experts proposed to change the term "non-alcoholic fatty liver disease" (NAFLD) to "metabolic-associated fatty liver disease" (MAFLD), which includes hepatic steatosis (HS) (using imaging or analytical scores) associated with overweight or obesity, type 2 diabetes (T2D), or the presence of two other metabolic disorders.
Objectives
Analyse the impact of bariatric surgery on MAFLD.
Methods
A total of 43 patients with obesity diagnosed with MAFLD were analysed before and 12 months after bariatric surgery. We compared body mass index (BMI), abdominal perimeter, body fat, HS, and liver fibrosis. HS was diagnosed using abdominal ultrasound and/or NAFLD Liver Fat Score (NAFLD-LFS: metabolic syndrome, T2D, plasma insulin, AST, and ALT). Liver fibrosis risk was assessed using NAFLD Fibrosis Score (NAFLD-FS: age, BMI, fasting glucose, AST, ALT, platelets, and albumin).
Results
Median pre-surgery age was 52 years (44-57), 51% were female. Median BMI was 42kg/m2 (40-43), median abdominal perimeter and body fat were 130 cm (122-139) and 37% (34-38) in males, and 123 cm (116-134) and 49% (45-50) in females. Regarding comorbidities, 72% had MS, 56% had T2D, 93% had HS identified with abdominal ultrasound and 98% using NAFLD-LFS. Hepatomegaly was observed in 56%. A high risk of fibrosis was calculated in 25%, no fibrosis risk in 19% and an indetermined score in 56%. Laboraty result revealed increased transaminases In 21%, increased gamma-GT in 30%, 2% thrombocytopenia, 5% hypoalbuminemia, and 2% hyperalbuminemia. After surgery, we observed 60.5% remission of MAFLD, with reduction in BMI (-13.2kg/m2, $P<0.001$), abdominal perimeter (-28cm in males and -25cm in females, $P<0.001$) and body fat (-19% in males and -15% in females, $P<0.001$). There was also 50% and 79% remission of MS and T2D, as well as 58% and 88% regression of steatosis and hepatomegaly in abdominal ultrasound, and 82% reduction of NAFLD-LFS steatosis. NAFLD-FS showed an overall reduction, with 60% at no risk and 40% with indeterminate scores after surgery. There was a significant reduction in platelet count (244x109/l (191-278), $P=0.002$), ALT (20U/l (14-33), $P<0.001$), gamma-GT (15U/l (11 -22), $P<0.001$) and insulin (6mU/ml (4-8), $P<0.001$), but no change in AST (19U/l (16-29), $P=0.125$), nor albumin levels (44g/l (43-46), $P=21$).
Conclusions
Following bariatric surgery, we observed similar outcomes in MAFLD as those described for NAFLD (66% remission). These results are associated with a significant improvement in comorbidities, with an overall reduction in liver fibrosis risk.

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P628

Features of the Course of Covid-19 in Patients With Metabolic Syndrome

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The COVID-19 pandemic has forced the dispatch of significant efforts to identify prognostic factors development of critical conditions and death. Elderly age, cardiovascular disease (CVD), blood sugar diabetes, chronic lung disease, arterial hypertension was associated with an increased risk of death with COVID-19. Metabolic syndrome is a significant comorbid pathology, which increases the risk of developing life-threatening complications and unfavorable outcome of the coronavirus infection. Due to this patient with metabolic syndrome and COVID-19 deserve especially close attention. One of the main constituents of MS are abdominal obesity. Obesity potentiates multiple cardiovascular risk factors, underlying clinical cardiovascular continuum, leading to the development of CVD and adverse cardiovascular outcomes. This association between obesity and severe COVID-19 infection may be due to increased expression of ACE-2 in overweight individuals, making it more likely that SARS-CoV-2 enters the body of obese individuals compared to non-obese individuals. ACE-2 is present in lung alveolar epithelial cells, small intestine epithelial cells, vascular endothelial cells, and adipose tissue, and its expression is increased due to obesity. Increased expression of ACE-2 can cause greater penetration of SARS-CoV-2 into the body, which can significantly increase the release of cytokines and lead to a fatal

outcome of COVID-19. Obese patients are more active nuclear transcription factor (NF) and higher RNA expression of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1(IL-1) and interleukin-6 (IL-6), which are key in the pathogenesis of the metabolic syndrome [15]. Also, the pro-inflammatory role of IL-6 is often described in the pathogenesis of lung diseases, especially in asthma and in patients with acute respiratory distress syndrome (ARDS). Understanding the relationship between obesity and severe course of COVID-19 may suggest some therapeutic interventions to potentially reduce the risk of developing adverse outcomes of COVID-19. This issue becomes especially relevant weight gain and changes in food intake.

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P629

The new anthropometric indices and atherogenic indices are correlated with lipid status in women with PCOS

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Introduction
Polycystic ovary syndrome (PCOS) contributes to endocrine and metabolic complications. Cardiovascular disease (CVD) is a leading cause of mortality and morbidity worldwide. Identification of the subpopulations with a higher risk of developing CVD and lipid metabolic disorders is crucial, particularly in PCOS patients.
Aim
The aim of this study was to investigate the usefulness of new anthropometric indices such as BAI, VAI, LAP, BRI, ABSI and new atherogenic indices such as TyG index, TyG-BMI index, TyG-WC index in evaluation of lipid parameters in patients with PCOS.
Material and methods
To the study was enrolled of 49 woman in aged 18-39. Criteria for selecting the subjects were as follows: diagnosed PCOS based on the Rotterdam criteria from 2003. Blood samples were taken from patients in the morning, before breakfast. Biochemical parameters (total cholesterol, HDL, LDL, TG) were determined and used for the calculation atherogenic indices. Anthropometric parameters were measured with the use of standard methods in the morning. These measurements included body weight, height, waist circumference, and hip circumference. After this step anthropometric indices such as BAI (Body Adiposity Index), VAI (Visceral Adiposity Index), LAP (Lipid Accumulation Product), BRI (Body Roundness Index), ABSI (A Body Shape Index), AIP (Atherogenic risk of plasma) were calculated. The study conformed to the Declaration of Helsinki and was reviewed by the local bioethics committee
Results
There was observed significant positive relationship between BAI, VAI, LAP, BRI, ABSI, TyG index, TyG-BMI index, TyG-WC index and LDL cholesterol and triglycerides ($P<0.005$). Also, there was observed strong negatively correlation between HDL cholesterol and analyzed parameters/indices ($P=0.000$) excluding ABSI ($P>0.05$).
Conclusion
Analyzed new anthropometric indices and new atherogenic indices have demonstrated significant relationship wtl lipid profile in women with PCOS. These indices may be useful tool in assessing of metabolic disorders in women with PCOS.

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Urinary C-peptide to creatinine ratio (UCPCR) as indicator for metabolic risk in apparently healthy adults - a BioPersMed cohort study

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Background
C-peptide consists of 31 amino acids, synthesized in the beta cells of the pancreas and co-secreted along with insulin. Hence, serum C-peptide may be the preferred diagnostic biomarker for evaluating beta cell function compared to insulin. The urinary C-peptide to creatinine ratio (UCPCR) recently gained attention as a non-invasive biomarker for evaluating and monitoring metabolic risk. In this study, we aimed to characterize guiding values of UCPCR in healthy individuals based on American Diabetes Association (ADA) criteria and follow-up outcomes in a large longitudinal cohort study.
Methods
Cross-sectional and longitudinal clinical and laboratory phenotyping including body composition and oral glucose tolerance tests of participants from the BioPersMed cohort (Biomarkers in Personalized Medicine) were evaluated. Our study population was based on ADA (American Diabetes Association) criteria defining non-diabetic subjects via fasting plasma glucose (FPG) $\leq$ 126 mg/ml ($\leq$ 7.0 mmol/l), 2-hour plasma glucose (2-h PG) of $\leq$ 200 mg/dl ($\leq$ 11.1 mmol/l) during 75-g oral glucose tolerance test (oGTT), and an HbA1c of $\leq$ 6.5% ($\leq$ 48mmol/mol). A two-site chemiluminescent sandwich immunoassay was used to detect urinary C-peptide levels, which were normalized by individual urinary creatinine values to obtain the ratio. Subjects were followed for 4.2 ± 0.62 years from baseline to their first and second biannual follow-up.
Results
Out of all BioPersMed participants ($n=1022$), 317 individuals were non-diabetic according to ADA criteria (female $n=198$ (62,5%), male $n=119$ (37,5%)) with a median age of 56 ± 8 years. In our study, we found no significant differences of UCPCR values between gender (*P*-value 0,997). During follow-up, initially healthy participants progressed by 25% to prediabetes and by 1% to type 2 diabetes mellitus (T2DM), predicted by UCPCR values.
Conclusion
UCPCR provides a valuable diagnostic biomarker for a non-invasive estimation of endogenous insulin production, which can be used to monitor and guide individual subjects over time for their potentially increased metabolic risk. A risk assessment graph for UCPCR ranges provides a useful screening and monitoring tool. UCPCR applications are not limited to T2DM but could further be used in other settings such as hyperinsulinemia in obesity or polycystic ovary syndrome (PCOS) and gestational diabetes

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Using digital technology to improve understanding and adherence of clinical guidelines for diabetic emergencies

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Background
Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) are common diabetic emergencies. However, the associated morbidity and mortality remains substantial. Non-specialist trainee healthcare professionals (HCPs) are usually the first point of contact in managing these patients in the acute medical setting. It is therefore essential that these trainees are confident in the management of these emergencies.
Aims
Our aim was to use digital technology to establish how confident trainee HCPs felt in managing diabetic emergencies, DKA and HHS, at a large university hospital Trust accepting unselected emergency cases. Digital platforms were utilised to assess trainees' understanding and access to national-based Trust guidelines for DKA and HHS.
Methods
An online survey was carried out between December 2022 and January 2023. A QR code was utilised to allow easy access to the survey. The code was disseminated via email, posters, and messaging platforms within our Trust.

Results
Data was gathered from 45 HCPs; 38% were foundation year 1 doctors, 42% were senior house officers, and the remainder were nursing staff, medical support workers or higher speciality trainees. 82% of the responders had managed DKA or HHS in the last 6 months. 91% of the HCPs knew where to access the online Trust guidelines and 85% of the responders regularly used these trust guidelines. However, the survey found that only 49% of responders felt confident in the management of DKA, and 31% felt confident in the management of HHS. With regards to insulin prescription, 31% did not follow guidelines in prescribing regular basal insulin alongside fixed-rate insulin in the management of DKA. Moreover, the vast majority (62%) were not confident at all with initiating basal insulin.
Conclusions
Digital technologies such as online surveys and QR codes allowed quick feedback to be gathered to assess the competency of non-specialist healthcare professionals in managing DKA and HHS. This survey showed that the majority of non-specialist trainee HCPs were aware of the guidelines for DKA and HHS, but were not confident in managing these diabetic emergencies. More than half of these trainees did not follow the guidelines especially in prescribing regular basal insulin. The results were used to improve the way guidelines are presented to non-specialist HCPs and to tailor teaching sessions for these trainees to improve their confidence in managing diabetic emergencies.

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Changing clinical features of diabetic ketoacidosis: any impact of SGLT2 inhibıtors is there?

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Aims
Sodium-glucose cotransporter-2 inhibitors (SGLT2i) increase the risk for diabetic ketoacidosis, particularly in patients with type 1 diabetes (T1DM). We aimed to determine whether SGLT2i use increase the risk of euglycemic diabetic ketoacidosis (euDKA) and to indicate its demographic, clinical features.
Methods
We performed a retrospective cohort study of 51 patients over 18 years-old admitted to emergency unit at a tertiary care hospital from 2018-2022. The data were collected by communicating with the hospital network system, national health registry, and personnel communication. Fisher's exact, Yates's chi-square, and Mann-Whitney-U tests were used to identify variables associated with euDKA initiation using SPSS-version23.
Results
We included 51 DKAs, of whom 33 (64.7%) were female out of 508 patients with hyperglycemia in the emergency department. T1DM, type 2 DM and latent autoimmune diabetes in adults (LADA) were present in 25 (49%), 22 (43.2%), and 4 (7.8%), respectively. 156 (30.7%) patients used SGLT2 and 19 (37.3%) of these patients were diagnosed with DKA. Regarding SGLT2i use there was no significant correlation between DKA and patients with non-DKA hyperglycemia ($P=0.364$). 15 and 4 patients with DKA had T2DM and LADA. SGLT2i use was significantly higher in patients with type 2 DM ($P<0.05$). All patients with LADA were using the SGLT2i which prescribed at different centres. The median age of patients using SGLT2i was 59.16 $\pm$ 17.63, BMI 25.09$\pm$4.80, plasma glucose 397.89$\pm$191.07, HbA1C 11.24$\pm$2.51, pH 7.17$\pm$0.16, HCO3 12.02$\pm$5.56. The mean age of patients using SGLT2i was significantly higher, plasma glucose levels were lower ($P<0.05$). There is a significant correlation between euDKA ($n=5$, 9.8%) and SGLT2i use ($P=0.005$). All 5 patients were using SGLT2i. There were 13 (25.4%) patients with urinary tract infection (UTI) of which 9 (69.2%) were female. The number of patients with any genitourinary infection (GUI) in women was 15 (45.5%). There was also a significant correlation between the use of SGLT2i and urinary tract infection (UTI), vulvavaginitis ($n=6$, 18.2%), GUI in women and in general ($n=19$, 37.3%) ($P=0.050$, $P=0.002$, $P=0.013$, $P=0.008$), respectively. In the euDKA group, 3 out of 5 patients required intensive care and one patient was dead.
Conclusions
We observed euDKA, DKA in T2DM and GUI (UTI or vulvavaginitis) cases were more common in patients using SGLT2i. Furthermore, we suggest that LADA should be excluded before starting SGLT2i. In sum, SGLT2i may increase the risk of the serious adverse events that should not overshadow the significant cardioprotective benefits and therefore carefully prescribed.

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The prevalence of vitamin D deficiency in hospitalized patients with COVID-19 decreased significantly during the pandemic in Slovakia between the years 2020-2022

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Background
The coronavirus disease 2019 (COVID-19) pandemic led to changes in lifestyle, which could influence vitamin D status on a population level. The purpose of our study was to compare 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalized because of severe COVID-19 during two waves of the pandemic (2020/21 vs. 2021/22).
Materials and methods
We analyzed 101 patients (61 males/ 40 females) hospitalized in the internal medicine department of University Hospital Bratislava during the third wave of COVID-19 pandemic (Group 2). The patients from the third wave of the pandemic were compared to 101 (61 males/ 40 females) sex and age-matched subjects from the second wave of the COVID-19 pandemic (Group 1). Patients were first matched for sex, then for age +/- 1 year. If several options were available for the match, patients with the closest value of BMI were chosen. Patients from both waves were hospitalized during the winter season: the second wave was considered from 1 December 2020 to 28 February 2021, and the third wave from 1 December 2021 to 28 February 2022. Both sexes were analyzed together, as well as separately. Analyses were also performed according to the age of the participants. Younger age was defined as <65 years, and older age was defined as $<$ 65 years. Serum 25(OH)D concentration $>$ 30 ng/ml was considered vitamin D sufficiency and concentration <20 ng/ml deficiency.
Results
The mean concentration of 25(OH)D on admission during the second wave of the pandemic (Group 1) was 17.76 ng/ml, which increased to 25.21 ng/ml during the third wave (Group 2) ($P<0.0001$). On admission, 82% of patients from Group 1 were 25(OH)D deficient, and 10% were 25(OH)D sufficient. In Group 2, 54% of patients were 25(OH)D deficient, and 34% of patients were 25(OH)D sufficient ($P<0.0001$). The proportion of patients with a history of vitamin D supplementation increased from 18% to 44% ($P<0.0001$). The most significant absolute change of 25(OH)D concentration between waves was observed in younger males (10,70 ng/ml, $P=0.002$), and the smallest absolute change of 25(OH)D concentration was observed in younger females (2,49 ng/ml, $P=0.676$). Serum 25(OH)D concentration higher by one ng/ml was associated with a ~ 7% increase in the chance of survival for given age and sex category.
Conclusions
The prevalence of inadequate vitamin D status in hospitalized patients with COVID-19 in Slovakia decreased significantly due to a higher rate of vitamin D supplementation during the COVID-19 pandemic.

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P634

Adverse impact of Covid-19 pandemic on the glycemic status of persons with diabetes: Experience from a large Indian cohort

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Introduction
There is a general assumption that glycemic control in persons with diabetes(PWD) has deteriorated since the onset of COVID-19 pandemic. We conducted this to compare the glycemic status of a very large cohort of PWD prior to COVID-19 outbreak with that of a similar cohort post onset of the outbreak.
Methods
This was a retrospective study wherein entire data of glycated hemoglobin (HbA1c)% available in the hospital database since 3rd October, 2017 till 31st Dec, 2021 were collected and segregated into two cohorts-one on or prior to 31st May, 2020(i.e., pre COVID-19) and another after 1st June (i.e., post COVID-19)
Results
Total 20575 HbA1c values (12081 in the pre COVID-19 arm and 8494 in the post COVID-19 arm) were used for analysis. Mean ($\pm$SD) HbA1c% in the post

COVID-19 arm (8.28 ± 1.9, 8) was significantly higher($P < 0.05$) than that of the pre COVID-19 arm (7.74 ± 1.33). The trend was consistent in various subgroup analyses such as males (8.33 ± 1.9 vs 7.73 ± 1.3)), females(8.21 ± 1.9 vs 7.75 ± 1.2), age <65 years (8.23 ± 1.9vs 7.72 ± 1.2) and age >65 years (8.13 ± 1.8 vs 7.9 ± 1.5). The main driver for such a difference was significantly higher numbers in the subcategory of HbA1c >10% ($P < 0.05$ compared to other categories) as clearly indicated in Table 1

Table 1 Total subjects in 5 different categories of HbA1c. Significance of each category is indicated in terms of *P*values.

HbA1c category	Pre Covid 19, n (%)	Post Covid 19, n (%)	P value
6%-6.9%	4170 (34.54)	2542 (29.96)	0.3 (NS)
7%-7.9%	3368 (27.9)	2061 (24.27)	0.4 (NS)
8%-8.9%	2204 (18.26)	1365 (16.07)	0.2 (NS)
9%-9.9%	1565 (13)	959 (11.3)	0.4 (NS)
≥ 10%	763 (6.3)	1562 (18.4)	≥ 0.05

Discussion
Our study and others suggested that the lockdown situation worsened the glycemic status of PWD.[1] Forced nationwide lockdowns could produce acute panic, anxiety and stress which may also lead to worsened glycemic status. [2]
Conclusion
COVID-19 pandemic has adversely impacted glycemic control in general amongst PWD in general.
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P635

Assesment the effects of long-term leptin replacement therapy on ocular structures in the patients with congenital leptin deficiency: a case-control study

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Purpose
Congenital leptin deficiency (CLD) is an extremely rare condition. The effects of the disease and leptin treatment on ocular structures are unknown in this patient group. In our study, we planned to compare the ocular findings of patients who received leptin replacement therapy due to leptin deficiency with the control group
Methods
In this prospective, cross-sectional comparative study, six patients with a diagnosis of congenital leptin deficiency and fifteen healthy controls were included. All participants underwent optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) imagining. Measurements of axial length, central corneal thickness, thickness of subfoveal choroid, retinal nerve fiber layer (RNFL) and macular vessel densities of the superficial capillary plexus and deep capillary plexus were compared.
Results
In the leptin group, 4 patients were on leptin replacement therapy for 23 years and two patients were on leptin replacement therapy for 4 years. The mean axial length ($P = 0.23$), anterior chamber depth ($P = 0.011$), and central corneal thickness ($P = 0.000$) measurements were significantly lower in the leptin group than the control group. The mean of subfoveal choroidal thickness (EDI) ($P = 0.002$), and nasal RNFL thickness ($P = 0.008$), were significantly increased in the leptin group. Perifovea superficial capillary plexus density were significantly decreased in the leptin group (45.02 ± 3.12) compared to controls (48.44 ± 3.61, $P = 0.005$).
Discussion
In this study, the ocular findings of patients with CLD and the effect of long-term leptin replacement therapy on ocular structures were evaluated for the first time in the literature. In our study, mean superficial retinal capillary plexus values of patients with congenital leptin deficiency were significantly lower than controls. The possible explanation for this result may be chronic hypoxia caused by inappropriate vascular structure and impaired angiogenesis due to leptin deficiency. In addition, the mean of EDI and nasal RNFL thickness measurements were significantly higher in leptin patients compared to controls. These results may be due to the effects of leptin on angiogenesis, cell proliferation, endothelial dysfunction, inflammatory and vascular smooth muscle proliferation. In addition, the increase in the nasal region RNFL layer thickness in the patient group, especially in those using leptin replacement therapy for more than 5 years, compared to the controls suggests the neuroprotective effect of leptin.
Conclusions
This study revealed that CLD can bring about developmental and pathological structural changes in anterior segment of eye and in vessel formation of retinal and choroidal vasculature.
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Time restricted feeding is a non-pharmacological strategy against diet induced obesity

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Background
Obesity is the major health problem in both developed and developing countries, due to increasing its rate there is a new strategy to prevent obesity by time restricted feeding (TRF). The aim of our study is the effect of TRF intervention on diet induced obese rats and their association with circadian gene expression.
Method
Total 15 Wistar rats were included in our study and divided into two groups. Control group and High Fat diet (HFD) group which consist of six rats and nine rats respectively. HFD group was fed fatty diet for two months to developed obesity. These rats were shifted to TRF with HFD for three months, after which they were again put back on *ad lib* (24 hr feeding). These rats were sacrificed and samples collected. Body weight was measured monthly, with blood glucose, Insulin, melatonin lipid profile and RNA expression estimated after sacrifice.
Results
The body weight and blood glucose level of HFD group were significantly increased as compared to control rats ($P = 0.0263$) and ($P = 0.0089$) respectively. The level of insulin, melatonin ($P = 0.006$) and HDL were reduced in rats fed with HFD whereas total cholesterol, TG and LDL were increased. TRF intervention reduced body weight, blood glucose level, TG, LDL Per1 expression and elevated the level of insulin, melatonin, total cholesterol, HDL and Bmal1 expression. TRF in HFD induced obesity showed its legacy effect when put on *ad lib.*
Conclusions
TRF is a potential behavioural intervention which is easily adaptable in lifestyle modification. TRF intervention can prevent and treat obesity and their associated disorders.
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Non-invasive methods of assessment of liver fibrosis in patients following chemotherapy

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Toxic hepatitis is a diffuse inflammatory process in the liver which is caused by the impact of industrial poisons of hepatotoxic action in doses exceeding the maximum allowable concentration. Given the complexity of differentiation, in fact, the symptoms of the disease from possible side effects of treatment, the statistics of the prevalence of the disease in this profile is quite ambiguous. Data from clinical studies show that in the structure of acute and chronic liver disease the drug lesions range from 0.7% to 20% and the percentage of all adverse reactions associated with the use of drugs ranges from 2% to 28%, 10% of which are cytostatic.
Aim
Of the work is to improve the possibility of diagnosing liver fibrosis due to its toxic lesion after chemotherapy in patients with normal weight and overweight by analyzing serum markers of fibrosis.
Materials and Methods
In dynamics, 88 people aged from 31 to 74 years with toxic liver damage without symptoms of cirrhosis and concurrent pathology of the liver and biliary tract were studied.

Results
All subjects were female (100%). The Fibrotest method was used to diagnose the stages of liver fibrosis. Analyzing the level of profibrogenic cytokine TGF-β_1 it was noted that the lowest value was 6123 ng/ml, the highest level was noted at 19746 ng/ml, with the average value for all examined patients was 12758 $\pm$ 3518.3. It was found to increase significantly with increasing stage of fibrosis and BMI with maximum values in the group of patients with toxic liver disease and obese. With the progression of liver fibrosis, the concentration of TGF-β_1 ($r=0.83$, $P<0.05$) in the blood increases, which confirms the role of TGF-β_1 in the activation of liver stellate cells and stimulation of collagen and other extracellular matrix synthesis and is likely a marker of the progression of fibrosing reactions. Also, direct strong correlations of TFG-β_1 with the stage of liver fibrosis according to the fibrotest ($r=0.88$, $P<0.05$).
Conclusions
The presence of excess body weight in cancer patients in stable remission correlates with the severity of liver fibrosis and may be an important factor in predicting the development of severe fibrosis in patients in the long term due to breast cancer treatment. The level of profibrogenic cytokine TFG β_1 correlates with the severity of liver fibrosis according to fibrotest and may be a sensitive predictor of fibrosis progression.

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Intake of Fruit and Glycemic Control in Korean Patients with Diabetes Mellitus

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Background
Despite the well-recognized health benefits of fresh fruit consumption, substantial uncertainties remain about its potential effects on glycemic control in patients with type 2 diabetes mellitus (T2DM).
Methods
We examined the association of fresh fruit consumption and glycemic control in patients with T2DM using data from the 7th Korea National Health and Nutrition Examination Survey. Study samples were divided into 3 groups based on the weekly fruit consumption frequency for the analysis.
Results
Patient with highest fruit intake were older compared to the other two groups and women were more likely to consume fruits. Fruit consumption was positively correlated with better HbA1c levels in these patients. Currents smokers and weekly alcohol intake also showed negative correlation according to the fruit intake tertiles. Moreover, patients with highest tertile of fruit intake were 3.63 times more likely to be in good glycemic control, meaning HbA1c <7% as shown in **Table 1**.

Table 1 Odds ratios for patients in good glycemic control (HbA1c <7%)

	Tertile 1	Tertile 2	Tertile 3
Crude model	1.00 (reference)	0.77 (0.45 – 1.34)	1.46 (0.84 – 2.55)
Model 1	1.00 (reference)	0.78 (0.45 – 1.35)	1.42 (0.81 – 2.48)
Model 2	1.00 (reference)	1.49 (0.62 – 3.59)	1.94 (0.79 – 4.77)
Model 3	1.00 (reference)	1.59 (0.67 – 3.81)	2.28 (0.88 – 5.89)
Model 4	1.00 (reference)	1.83(0.69 – 4.88)	3.63 (1.20 – 11.03)

Model 1 is adjusted by sex and age Model 2 is adjusted by sex, age, body mass index, systolic blood pressure, Triglycerides, LDL-C, current smoking and alcohol intake Model 3 is adjusted by Model 2 plus total energy intake Model 4 is adjusted by Model 3 plus walking per week and dietary fiber intake

Conclusion
In this study, we observed a significant beneficial impact of fruit consumption on glycemic control in Korean patients with T2DM.

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P639

Abstract withdrawn

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Angiotensin-Converting Enzyme (ACE) Level, But Not ACE Gene Polymorphism, Is Associated with Prognosis of COVID-19 Infection: Connection Between Type 2 Diabetes, Hypertension and Renin-Angiontensin-Aldosteron System

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Introduction
Renin-angiotensin-aldosterone system was shown to be activated in severe COVID-19 infection. We aimed to investigate the relation between angiotensin converting enzyme (ACE) levels, *ACE* gene polymorphism, type 2 diabetes (T2DM), and hypertension (HT), and the prognosis of COVID-19 infection.
Methods
Clinical features of adult patients with SARS-CoV-2 infection diagnosis were analyzed. *ACE* gene analysis and ACE level measurements were performed. The patients were grouped according to *ACE* gene polymorphism (DD, ID or II), disease severity (mild, moderate, or severe), and the use of dipeptidyl peptidase-4 enzyme inhibitor (DPP4i), ACE-inhibitor (ACEi) or angiotensin receptor blocker (ARB). Intensive care unit (ICU) admissions and mortality were also recorded.
Results
A total of 266 patients were enrolled. Gene analysis detected DD polymorphism in *ACE I* gene in 32.7% ($n=87$), ID in 51.5% ($n=137$), and II in 15.8% ($n=42$) of the patients. *ACE* gene polymorphisms were not associated with disease severity, ICU admission, or mortality. ACE level was higher in patients who died ($P=0.004$) or admitted to ICU ($P<0.001$), and in those with severe disease in comparison to mild ($P=0.023$) or moderate ($P<0.001$) cases. HT, T2DM, and ACEi/ARB or DPP4i use were not associated with mortality or ICU admission. ACE levels were similar in patients with or without HT ($P=0.374$) and with HT using or not using ACEi/ARB ($P=0.999$). It was also similar in patients having T2DM or not ($P=0.062$) and in those with T2DM under DPP4i or not ($P=0.427$) . ACE level was a weak predictor of mortality, but an important predictor of ICU admission. ACE level predicted ICU admission in total (cut-off value >37.092 ng/ml, AUC:0.775, $P<0.001$).
Conclusions
Our findings suggest that higher ACE levels, but not *ACE* gene polymorphism or ACEi/ARB or DPP4i use, were the associated with the prognosis of COVID-19 infection. Presence of HT and T2DM, and ACEi/ARB or DPP-4i use was shown not to be associated with mortality or ICU admission.

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Table 1 (Abstract P640) ROC analysis showing cut-off values for ACE levels predicting ICU admission in different groups.

	ICU admission		ACE Cut-off	Sensitivity	Specificity	AUC(SE.)	p
	Absent	Present					
HT (-)	131	17	26.1125	70.0%	80.0%	0.777(0.084)	**0.004**
HT (+) ACEi/ARB (+)	66	8	38.7225	50.0%	93.0%	0.705(0.124)	0.106
HT (+) ACEi/ARB (-)	36	8	18.553	100.0%	51.7%	0.779(0.092)	**0.049**
T2DM (-)	171	20	26.098	70.0%	77.7%	0.768(0.086)	**0.005**
T2DM (+) DPP-4i (-)	50	9	17.9445	100.0%	41.0%	0.634(0.096)	0.264
Total	233	33	37.092	92.5%	52.4%	0.775(0.053)	**<0.001**

P641

Cancer, cardiovascular disease and all-cause mortality in Iraqi- and Swedish-born individuals in Sweden - the MEDIM cohort study

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Background
Immigrants from the Middle East to Sweden have a twice as high prevalence of type 2 diabetes (T2D) and obesity as native-born Swedes. Both obesity and T2D have been linked to increased incidence of cancer, cardiovascular disease (CVD) and all-cause mortality (ACM); however, data on differences between ethnicities are scarce.
Aims
In a population-based cohort we aimed to study the impact of Middle Eastern and European ethnicity on ACM, cancer- and CVD related mortality, incidence of cancer and CVD in an eight-year follow-up study. Methods: People born in Iraq or Sweden, who were 30-75 years of age, were invited from 2010-2012 to participate in the population based MEDIM study. A total of 1398 Iraqi- and 757 Swedish-born residents participated in the study, which consisted of a health exam, fasting blood sampling, assessment of insulin secretion and action (through oral glucose tolerance test) and questionnaires assessing history of CVD, cancer and T2D. Register data were retrieved until the 31st of December 2018 from the Swedish National Patient Register and Cause of Death register regarding CVD diagnosis, cancer diagnosis and cause of death. Information regarding diabetes (DM) diagnosis was retrieved from the National Diabetes Register. Individuals with a history of cancer or CVD at baseline were excluded. Cox regression analysis was assessed to study the adjusted hazard ratios (HR) for the relationships between ethnicity and ACM, cancer events, CVD events, death from cancer, and death from CVD, with adjustments for age, sex, anthropometrical measures, DM, and lifestyle.
Results
The HR for ACM was 0.35 (95% CI .14-.86) (p0.05) were observed for CVD related morbidity and mortality between Iraqi- and Swedish-born.
Conclusion
In this 8-year follow-up study, our data show that despite the high burden of cardiovascular (CV) risk factors and T2D, ACM, cancer morbidity and mortality rates were lower in Iraqi-born immigrants compared to native Swedes.

Keywords
Immigrants · Cancer · Middle East · Mortality · CVD · Type 2 diabetes

Abbreviations
ACM, all-cause mortality; CV, cardiovascular; CVD, cardiovascular disease; T2D, type 2 diabetes; DM, diabetes mellitus; PA, physical activity; ICD, International Classification of Disease; BMI, body mass index; LD, low-density lipoprotein; HDL, high-density lipoprotein; ISI, insulin sensitivity index; DIO, oral disposition index; SD, standard deviation; IQR, interquartile range

Funding
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P642

Abdominal pain in pediatric diabetic ketoacidosis: a single center study

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Background
Despite typical constitutional findings (polyuria, weight loss, and polydipsia), clinical presentation of diabetic ketoacidosis also includes nausea, frequent vomiting and abdominal pain. Moreover, diffuse abdominal tenderness and diminished or absent peristalsis might mimic acute abdomen in pediatric patients. There is paucity of published data regarding prevalence, dynamics and associated laboratory findings in pediatric patients with abdominal pain in DKA.
Aim
To evaluate prevalence of abdominal pain in pediatric DKA; compare and correlate clinical and laboratory findings between children with and without abdominal pain in DKA.
Materials and methods
Ninety-nine pediatric patients' records with diagnosis "diabetic ketoacidosis" on admission from January 2016 to December 2021 were screened for this retrospective single center study. Primary inclusion criteria of DKA were met by 58 pediatric patients (pH $<$ 7,3; blood sugar $\geq$ 11mmol/l; urine ketones $>++$; negative diagnostic abdominal ultrasound). Additionally we included 22 patients transported from the low resource hospital settings (pH was not measured initially) according to the standard patient pathway. These patients had already received initial resuscitation upon admission to our settings and showed improved blood sugar and pH levels. Thus, exclusion criteria of this subgroup included pH>7,35, urine ketones $<++$, with no regards to blood sugar upon secondary check-up. All patients (age range -3-17 yo) were divided into two groups: control – patients without abdominal pain ($n=53$), study grou*P*– patients with abdominal pain ($n=27$). Initial work-up included HbAc1, pH, electrolytes, CBC etc. The local institutional bioethics committee approved the study design.
Results
Prevalence of abdominal pain was 36% (13/36) and 32% (14/44) in new onset T1DM and previously confirmed diabetes (OR: 1.2112; CI 95% [0.4779 - 3.0699], $P=0.6864$. Tenderness upon palpation of the LUQ and periumbilical region was elicited among 59% (16/27) and 18.5% (5/27) of patients, respectively. Mean pH upon admission was 7.16 ± 0.15 and 7.19 ± 0.11 among the controls and the study group, respectively ($P=0.2901$). HbAc1 ranged from 7 to 17,5% (controls – $12.62\pm2.09\%$; the study group $-12.41\pm2.4\%$, $P=0,6998$). Leukocytosis was found in both groups (controls $-16.09\pm8.81*10^9$/l; the study group $-15.85\pm6.75*10^9$/l, $P=0,9013$). 71% (5/7) of patients with severe DKA, 31% with moderate (12/39) and 35% (7/20) with mild DKA suffered from abdominal pain. No significant associations between DKA severity and presence of abdominal pain were observed.
Conclusions
One in three pediatric patients experience abdominal pain in DKA. This clinical finding is not associated with severity of DKA, pH level, WBC count and HbAc1 in children with negative diagnostic abdominal ultrasound.

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P643

Physical activity assessment is crucial for obesity risk prediction in adolescent patients

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Physical activity is assumed to be a factor of great importance for weight maintenance. Assessment of physical activity in childhood should be done for identifying patients at risk and predicting obesity development. The aim of our study was to assess physical activity's importance as a risk factor for weight changes in boys and girls 8-18 years aged. The study include 262 subjects (128 boys, 134 girls) in single country region in Bulgaria (mean age 12.02 ± 3.03 years, mean BMI 20.38 ± 4.36 kg/sq.m). Children were asked to answer unified questions considering information about physical activity (time spent in sport, open air activities and before screen time). The information was assessed regarding BMI and weight problems. Results show that 26.87% of girls and 17.19% of boys have previous problems with body weight and 10.45% of girls and 10.93% of boys have increased body weight at the moment. Two girls (1.49%) and six boys (6.25%) were diagnosed with obesity. BMI showed negative correlation with average time spent in physical activity ($r=-0.301$) and open-air activities ($r=-0.321$) and positive correlation with before screen time ($r=0.274$). No other correlations between healthy and unhealthy activity habits were established. No differences in gender and age were found. Based on our data we found out that physical activity assessment is of great importance for adolescent weight gain and risk of obesity. The increase in active sport activity and decrease of before screen time is crucial for weight maintenance and should be focused by parents in establishing of daily child's habits

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P644

Evaluation of the Frequency of Exocrine Pancreatic Insufficiency in Patients With Diabetes Mellitus

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Introduction and Aim
In our study, the frequency of exocrine pancreatic insufficiency, and its relationship with the duration of diabetes and the level of glycemic control and other complications of diabetes were investigated in patients with diabetes mellitus.
Materials and Methods
This paper was supported by Manisa Celal Bayar University Scientific Research Projects Coordination Unit, Project Number 2021-086. A total of 249 diabetic patients, 21 with type 1 diabetes mellitus, 2 with MODY, and the remaining 226 with type 2 diabetes mellitus, were included in this prospective study, between 15 September 2021 and 20 September 2022. The frequency of exocrine pancreatic insufficiency was investigated using fecal elastase-1 measurements in stool. Statistical evaluations were made with T test, Chi-square test and Kruskal Wallis test.
Results
In 20 patients, fecal elastase-1 levels were below 100 mg/ml and this was considered as severe exocrine pancreatic insufficiency. In 57 patients, fecal elastase-1 levels were found to be between 100-200 mg/ml and it is evaluated as mild-moderate exocrine pancreatic insufficiency. In total, exocrine pancreatic insufficiency was detected in 77 patients (30.9%). While mean duration of diabetes mellitus in 77 patients with exocrine pancreatic insufficiency was 11.34 ± 9.42 years, the mean disease duration of 172 patients with normal fecal elastase levels was 9.06 ± 7.81 years. The difference was found to be statistically significant ($P = 0.047$). When glycemic control, duration of diabetes mellitus and exocrine pancreatic insufficiency were evaluated, exocrine pancreatic insufficiency was found more frequently in patients with HbA1c level above 8.5% ($P = 0.007$) and in patients with diabetes mellitus for more than 15 years ($P = 0.018$). In addition, when diabetes mellitus complications and exocrine pancreatic insufficiency were evaluated, exocrine pancreatic insufficiency was found more frequently in patients with diabetic retinopathy ($P = 0.033$). No relation was found between neuropathy, nephropathy and coronary artery disease.
Conclusions
In our study, it was revealed that exocrine pancreatic insufficiency was more common as the duration of diabetes increased and glycemic control worsened. Exocrine pancreatic insufficiency was also found more frequently in patients with diabetic retinopathy. Although it is thought that exocrine pancreatic insufficiency may be one of the chronic complications of diabetes mellitus, further studies with more patients are needed.
Key words
Diabetes mellitus, Exocrine Pancreatic Insufficiency, Fecal Elastase.
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Epidemio-clinical and microbiological profile of Staphylococcus aureus bacteremia in diabetics

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Purpose
Diabetes is a major risk factor for Staphylococcus aureus (SA) bacteremia. The purpose of this work is to study the epidemiological, clinical and microbiological profile of SA bacteremia in diabetics.
Patients and methods
Retrospective study conducted in the infectious diseases department of Sfax between January 2003 and April 2022 (19 years), including all diabetics admitted for SA bacteremia (at least one positive blood culture).
Results
Among 166 patients admitted for SA bacteremia, 72 were diabetic (43.3%). They were 38 men and 34 women, with an average age of 53 ± 19 years. Associated risk factors were catheterism ($n = 27$) and surgery ($n = 8$). Bacteremia was community-acquired ($n = 38$) and nosocomial ($n = 34$). The portal of entry was mainly endovascular ($n = 29$) and cutaneous ($n = 28$). Septic localizations were noted in 37 cases (51.4%), mainly bone ($n = 17$), muscle ($n = 10$), lung ($n = 7$), joint ($n = 7$), kidney ($n = 6$) and neurological ($n = 6$). Community strains and nosocomial strains were resistant to methicillin in 18% and 29% respectively. Antibiotic susceptibility was for fusidic acid (81%), rifampicin (80%), gentamicin (80%), ciprofloxacin (78%) and cotrimoxazole (69%). The mean duration of antibiotic therapy was 54 ± 30 days. The evolution was favorable in 96%.
Discussion
SA bacteraemia is frequent in diabetics and is characterized by the multitude and variety of septic localizations. SA meti-R is relatively common in nosocomial and community settings. Early and appropriate antibiotic therapy often guarantees a good evolution.
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P646

A Case of Diabetes Mellitus Following the COVID-19 Vaccine

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A Case of Diabetes Mellitus Following the COVID-19 Vaccine
Background
Coronavirus disease-2019 (COVID-19) is a public health issue worldwide. Although COVID-19 vaccines are one of the most effective strategies against COVID-19, it has been reported in recent publications that they can trigger endocrine diseases. Herein, we aimed to present a 37-year-old male patient who had polydipsia, polyuria, thirst, fatigue, and loss of appetite a month after the first dose of the COVID-19 RNA-based vaccine without a prior history of diabetes mellitus.
Case report
A 36-year-old male patient was admitted to the emergency department with complaints of polyuria, polydipsia, thirst, anorexia, and fatigue, which occurred a month after the first dose of the COVID-19 RNA-based vaccine. He had no medical history. Hyperglycemia (645 mg/dl), metabolic acidosis (pH 7.3), and ketonuria were detected in laboratory analysis. The glycated hemoglobin (HbA1c) level was elevated (Table 1). He was diagnosed with diabetic ketoacidosis and management was initiated with intravenous fluid replacement and insulin infusion. When ketoacidosis resolved, subcutaneous multiple daily injections of insulin was initialized. In the follow-up, the patient's insulin therapy was discontinued, and he was discharged with vildagliptin 100/mg/day and metformin 2000 mg/day treatment. The HbA1c level was 10.4%, and the c-peptide level was 4.04 ng/ml six months after the diagnosis. Pioglitazone 30mg/day was added to the patient's treatment. The patient's follow-up continues in our center.
Conclusions
Recent studies have been reported that COVID-19 vaccination induced hyperglycemia and related complications. In general, the majority of patients presented with common osmotic symptoms of hyperglycemia. In most cases, good glycemic control was attained in patients on oral antidiabetic medication after discharge. As the vaccination of the global population accelerates, there must be an investigation of the side effects of COVID-19 vaccines. So that subjects at risk for diabetes can be predicted and appropriate treatment initiated without severe complications.

Table 1 Laboratory analysis of patient at the time of admission

	Values	Reference range
Fasting plasma glucose (mg/dl)	645	74-100
HbA1c (%)	18.1	3.5-5.6
Creatinine (mg/dl)	0.75	0.7-1.2
C-reactive protein (mg/l)	1.72	0-5
Sedimentation rate	13	0-20
Sodium (mmol/l)	120	136-146
Potassium (mmol/l)	4.34	3.5-5.1
Calcium (mg/dl)	9.58	8.6-10.2

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P647

New onset diabetes mellitus and thyroid dysfunction following Prembolizumab – a case report

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Introduction
Prembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, is one of the immune checkpoint inhibitors (ICI) that have revolutionized cancer therapy. However, ICIs can also trigger immune-related adverse events (irAEs) in different organ systems, including endocrine glands. While thyroid dysfunction is among

the most common endocrinopathies reported, ICI-induced diabetes mellitus (DM) is extremely rare, with an overall incidence ranging from 0.9 to 2%.
Case report
We report the case of 76 years-old woman, with past history of hypertension and dyslipidemia. She was diagnosed in August/20 with an endometrial adenocarcinoma with peritoneal dissemination. In September/21, due to disease progression, she started treatment with Prembolizumab. A month later she developed a transitory thyrotoxicosis, followed by permanent hypothyroidism, most likely caused by silent inflammatory thyroiditis and is currently being treated with levothyroxine. About 6 months later, her fasting blood glucose levels (108 – 119mg/dl) and her A1c levels started to rise (5.8 - 6.3%). Since she was asymptomatic, she was started on SGLT2 inhibitor treatment. Nevertheless, two months later, she suddenly started to lose weight and complaining of polyuria and polydipsia. At observation, she had a blood glucose level of 477mg/dl, positive ketones (4.5mmol/l) and a metabolic acidosis. A diabetic ketoacidosis (DKA) was admitted, and she was treated accordingly. Her laboratory results at that time revealed an A1c level of 9.6% and a low C-peptide (0.44ng/ml). ICI-induced DM was admitted, and a basal-bolus insulin scheme was started. Prembolizumab treatment was never stopped, and she has been gradually improving her metabolic control.
Conclusion
ICIs are associated with significant endocrine irAEs, that can appear at anytime throughout the course of ICI treatment. In the case reported, two endocrinopathies appeared progressively, with a thyroiditis presenting right after the beginning of ICI treatment and a DM appearing about 6 months later. The majority of patients with ICI-induced DM presents in a fulminant way and DKA is frequent at diagnosis, seen in up to 70% of cases. In the reported case, both the high A1c level at DKA diagnosis and the previous signs of glucose metabolism dysfunction, suggest a slower DM development than what is usually described. Nevertheless, our patient ended up presenting with DKA and will probably need lifelong insulin replacement. Although rare, ICI-induced DM can be life-threatening, and a prompt diagnosis is essential. This reinforces the importance of patient education and regular endocrine dysfunction monitoring as a key to reduce irAEs impact.

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Five-year trends of Turkish nationwide survEy of glycemic and other Metabolic parameters of patients with type 2 Diabetes (TEMD-2 study), 2017-2022

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Objective
Establishing good metabolic control is essential to prevent morbidity and mortality in patients with type 2 diabetes (T2DM). This nationwide survey is performed five years after the first national TEMD study, to search for any improvement in attaining glycemic and metabolic targets in Turkish patients with T2DM.
Methods
The nationwide, multicenter survey consecutively enrolled patients who were under follow up for at least a year in tertiary centers specialized for diabetes care. Optimal control was defined as HbA1c $<7\%$, home arterial blood pressure (ABP) $<135/85$ mmHg, or LDL-C <100 mg/dl or <70 mg/dl or <55 mg/dl according to the risk factors of patients.
Results
A total of 4956 patients (female 2965 (59.8%); median age (IQR) 59(13) years) were enrolled. The clinical and sociodemographic characteristics of patients in previous and current surveys are given in table. The recent survey showed that HbA1c levels are significantly higher, and the HbA1c target attainment rates are poorer ($P<0.001$ for both). Also, mean BMI, systolic and diastolic ABP, and LDL-C levels were significantly lower ($P<0.05$ for all). Macrovascular complication rates were similar while nephropathy rates increased and retinopathy and neuropathy rates decreased in the recent survey ($P<0.001$ for all).
Conclusion
The results of the TEMD-2 Survey show that the glycemic control rates were poorer while other metabolic parameters (BMI, blood pressures, LDL-C) were better five years after the first TEMD survey.

Table Comparison of clinical and sociodemographic characteristics of patients with Type 2 diabetes of TEMD-1 Study (2017) and TEMD-2 Study (2022)

Variable	TEMD-1 ($n=4756$)	TEMD-2 ($n=4956$)	p
Age, years, mean±SD	58.5±10.5	58.9±10.0	**0.030**
Gender (female), n (%)	2799 (58.9)	2965 (59.8)	0.332
Diabetes duration, years, mean±SD	10.9±7.5	13.1±8.1	**<0.001**
BMI, kg/m^2, mean±SD	32.1±6.5	31.7±6.6	**0.002**
SBP (home), mmHg, mean±SD	125.8±13.7	124.8±13.6	**0.004**
DBP (home), mmHg, mean±SD	77.6±8.8	76.9±9.0	**0.002**
HbA1c, %, mean±SD	7.7±1.7	7.9±1.9	**<0.001**
LDL-C, mg/dL, mean±SD	113.9±36.2	109.5±41.0	**<0.001**
HDL-C, mg/dL, mean±SD	46.5±12.9	47.9±13.6	**<0.001**
Triglyceride, mg/dL, mean±SD	182.1±128.7	178.2±130.6	0.141
eGFR (ml/min/1.73m^2), mean±SD	87.4±29.9	85.7±27.6	**0.006**
Macrovascular complications, n (%)	1152 (24.2)	1266 (25.5)	0.133
Microvascular complications, n (%)	2258 (47.5)	2541 (51.3)	**<0.001**
Obesity (BMI ≥30 kg/m^2), n (%)	2749 (58.6)	2717 (54.8)	**<0.001**
Achieving Targets			
BMI < 30 kg/m^2, n (%)	1945 (41.4)	2238 (45.2)	**<0.001**
LDL < 100 mg/dL, n (%)	1679 (37.3)	2184 (44.1)	**<0.001**
HbA1c < 7%, n (%)	1857 (40.0)	1819 (36.7)	**0.001**
Regular exercise, n (%)	1513 (31.8)	2077 (41.9)	**<0.001**

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Serum Follistatin-Like-1(FSTL-1) Levels in Gestational Diabetes and The Role of FSTL-1 Gene Polymorphism in the Development of Gestational Diabetes Mellitus

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Introduction
Gestational Diabetes Mellitus (GDM) is associated with maternal and perinatal morbidity. Follistatin-like 1 (FSTL-1), also known as TGFB-beta-stimulated clone 36 (TSC-36), is a glycoprotein cardiokine reported to be associated with insulin resistance and inflammatory processes. To date, there is no study evaluating the effect of FSTL-1 gene polymorphism on the development of GDM in the literature. In this study, we aimed to investigate the effect of serum FSTL-1 level and FSTL-1 gene rs12173 and rs869247 polymorphism in the development of GDM.
Material and Method
Demographic characteristic sand metabolic parameters (FSTL-1, fasting plasma glucose, fasting insulin, HbA1c) of all participants were evaluated. DNA was isolated from peripheral blood. Genotype and allele frequencies were determined by PCR-RFLP method. The prevalences of FSTL-1 polymorphism of the patient sand controls were compared.
Results
72 patients with GDM (meanage: 29.54±4.56 years) and 79 healthy pregnant women (meanage: 28,27±4,47 years) were included in the study. GDM patients had significantly higher BMI than the control group (27.44±5.46 kg/m2 vs. 25.39±2.96 kg/m2, $p<0.001$). The mean HbA1c % in the GDM group was found to be higher than in the control group (5.11±0.42% vs. 4.92±0.30%, p=0.002).There was no significant difference in the serum FSTL-1 levels between the groups (339.35±293.59 ng/mL for GDM and 414.53±364.09 ng/mL for control group; p=0.917). 11 GDM patients (15.3%) had CC genotype, 22 (30.6%) had CT genotype, and 39 patients (54.2%) had TT genotype of FSTL-1 gene rs12173 polymorphism. The prevalence of CC-, CT- and TT- genotypes, in the control group was 11.4, 20.3, and 68.4% respectively-similar prevalences as in the patient group (p:0.097). 24 GDM patients (33.3.%) had CC genotype, 38 (52.8%) had CT genotype, and 10 patients (13.9%) had TT genotype of FSTL-1 gene

rs869247 polymorphism. There was no difference in the distribution of the genotypes of FSTL-1 gene rs869247 polymorhism between the groups (24.1, 65.8, and 10.1%forCC-, CT- and TT- genoypes, in the control group, p: 0.264). There was no difference in the allele frequencies of FSTL-1 gene rs12173 and rs869247 polymorphism between the groups (p=0.086 andp=0.627, respectively).
Conclusion
FSTL-1 gene rs12173 and rs869247 polymorphism seemed to have no effect on the development of GDM. Large-scale studies are needed to find out the molecular mechanisms of FSTL-1 on metabolic diseases

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P650

Insulin adherence in type 1 diabetes: about 69 cases (Preliminary results)

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Introduction
Insulin, an essential treatment for type 1 diabetes, must be implemented as soon as diabetes is discovered. It helps to ensure glycemic control. Poor therapeutic compliance may be responsible for the development and progression of complications related to glycemic disorders.
Objective of the study
Assess insulin adherence in type 1 diabetes and study the consequences on glycemic control.
Materials and methods
This is a descriptive prospective study in a group of type 1 diabetic patients followed in the endocrinology and metabolic diseases department at the UHC Ibn Rochd in Casablanca from September 2022. The evaluation of therapeutic compliance was evaluated by the Morisky-Green questionnaire "high adhesion if the score is greater than or equal to 8, medium adhesion between 6 and 7 and low adhesion if <6". Statistical analysis was performed using SPSS 25.
Results
We included 69 patients. The average age was 25 years (+-6.7 years). There is a male predominance with 38 patients (55.1%). Among these patients, 39.1% had a college education level, 29% a high school education level and 7.2% university. The socio-economic level was low in 62 patients (89.9%). The average duration of diabetes was 11.51 years (+-6.4 years). Almost all of our patients were on a basal-bolus regimen (91.3%) including 52 patients (75.4%) on human insulins and 17 patients (24.6%) on insulin analogues. The average number of injections per day was 4.7. The average HbA1c was 10.32% (+- 2.4%). Adherence to insulin was good in 52.2% of cases, medium in 27.5% of cases and low in 20.3% of cases. In bivariate analysis, patients with good treatment compliance had an A1c within the target ($P=0.005$). In multivariate analysis, patients with poor adherence to treatment were more at risk of microangiopathic complications ($P=0.038$).
Conclusion
Therapeutic compliance was low in 20.3% of cases, which suggests the importance of therapeutic education of these patients and the need to create specialized education units.

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Endocrine-related Cancer

P106

Ectopic Cushing syndrome due to a late metastatic recurrence of a salivary gland carcinoma: a new therapeutic approach

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Background
Acinic cell carcinoma of the parotid gland is a rare cancer, and metastatic (M1) disease is uncommon, occurring in around 10% of cases, with ectopic paraneoplastic Cushing being described in only few cases.
Clinical case
A 58-year-old woman, with a history of dedifferentiated parotid acinar cell carcinoma, underwent surgery and adjuvant radiotherapy in 2005. In February 2019 the disease recurred with pulmonary, bone and lymph node metastases. Despite further 4 lines-oriented chemotherapies disease showed liver progression. April 2022, facial edema, asthenia, muscle weakness, skin fragility and hyperpigmentation and worsening of blood pressure control with abdominal obesity and hypokalemia established. Clinical suspicion of ACTH dependent Cushing's syndrome was confirmed by the biochemical studies: ACTH 1174pg/ml, plasma cortisol 59 mg/dl, urinary free cortisol (UFC) 2046 mg/24h (1633 mg/24h by mass spectrometry), 8 mg dexamethasone test: cortisol: 27 mg/dl. Pituitary MRI was negative for adenoma and 68Ga-DOTATE- PET scan was positive for all M1, suggesting positive somatostatin receptors. PET-FDG showed similar distribution of the radiotracer. Biopsy of the new liver M1 shows a high-grade carcinoma, Ki80%, and a positive ACTH in 10%, as well as positive expression of somatostatin receptors 2 and 5. Treatment of the hypercortisolism with the steroid inhibitor Osilodrostat was started in rapidly ascending doses to 10mg c/12h, with rapid and stable decrease of cortisol at basal values of 26 mg/dl with a UFC of 416 mg/24 h after 4 weeks of treatment with control of hypertension and of the Cushing phenotype. K and oedema were controlled by adding mineralocorticoid antagonists. Two doses of PRRT with Lu177-DOTATATE were administrated at external center with significant reduction of the liver M1. Intercurrence of urinary sepsis with hypotension in context of self-overdosing of analgesic treatment required parenteral glucocorticoid administration, and finally block and replace treatment was selected (UFC at hospital discharge was of 268 mg/24 h with cortisol of 7 mg/dl y under concomitant dexamethasone 2 mg/day). Unfortunately, despite biochemical stability during 3 months of Osildrostat and partial response to the PRRT the clinical condition acutely worsted due to spinal cord compression and palliative treatment was initiated.
Conclusion
Hereby we show the clinical case and therapeutic approach of a salivary carcinoma with metastatic late recurrency after more than one decade with ectopic ACTH secretion.

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P107

Congenital craniopharyngioma – Cases recruited in the German Kraniopharyngeom trials and review of the literature

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Background
Craniopharyngiomas (CP) are rare malformational tumors. Clinical presentation and outcome of patients with congenital CP (cCP) are not clear and refer mainly to few case reports in the literature. The aim of this study was to analyze clinical presentation and outcome in patients with cCP.
Clinical cases
Seven hundred and nine patients diagnosed with adamantinomatous CP were recruited 1999-2021 in HIT-ENDO, KRANIOPHARYNGEOM 2000 / 2007 / Registry 2019 and prospectively observed. In 3 cases, cCP was diagnosed prenatally and in one case at the 2nd day of life. Pre- and perinatal diagnostic findings, postnatal evaluation, therapeutic interventions and outcome in these 4 cases of cCP were analyzed. When compared to cases of cCP reported in the literature, more recent cases like our reported cCP have an overall better prognosis with regard to survival and sequelae. Two of our 4 cCP suffered from hemiparesis and one patient presented with mild motor retardation. In contrast to historical reports (lethal rate of $>50\%$), all patients in our report recruited after 2000 survived. Prenatal routine ultrasound examination was the usual diagnostic procedure leading to diagnosis of cCP. Tumor resection was performed during early postnatal period (range: 11 - 51 days of age). Complete resection of the mostly large sized tumors could be achieved in two of four patients with cCP.
Conclusions
Based on improvements of diagnostic and therapeutical methods and techniques, earlier prenatal diagnosis of cCP should lead to intrauterine transfer of cCP patients to a specialized center for postnatal treatment of newborns with sellar masses by a multidisciplinary team to secure an improved prognosis of these patients.

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P108

Hypothalamic-pituitary endocrine surveillance among childhood and young-adult cancer survivors

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Introduction
Survivors of childhood, adolescent or young adult cancers are at risk of endocrine dysfunction from their tumours, surgery, chemotherapy and/or radiotherapy treatment. The hypothalamic pituitary axes and gonads are at risk of dysfunction depending on a number of risk factors. Endocrine dysfunction can occur from before diagnosis of cancer, soon after but mostly a number of years later, even after survivors have been discharged from oncology follow-up. We aim to evaluate the burden of endocrinopathies and tempo of hormonal losses during long-term follow-up in survivors.
Methods
All patients currently attending our Late Effects Endocrine Clinic (LEEC) were included and following data extracted from notes: demographics, primary tumour, cancer therapy received, endocrinopathies along with year of diagnosis.
Results
137 patients are currently under long-term follow-up in LEEC, with a F:M of 1:2. 75% of patients had previous solid intracranial tumours and 15% suffered from haematological malignancies. Mean age at diagnosis of cancer was 17 years with 80% diagnosed before 20 years of age. Mean duration of follow-up is 18 years. Treatment modalities for cancer included surgery (50%), cranial radiotherapy (85%), spinal radiotherapy (25%) and chemotherapy (60%). 7% of patients had four anterior pituitary hormone deficiencies (thyroid, steroid, gonadal and growth hormone). 70% of patients had up to 3 hormone deficiencies and 23% had none. Notably 36% of eugonadal patients had steroid and/or adrenal deficiency. Overall hormonal losses mostly occur between 6 and 15 years post cancer treatment. Adrenal deficiency occurred mostly soon after cancer treatment with no further loss after 10 years of follow-up. Thyroid deficiency occurs progressively during the first 15 years of follow-up. In contrast, gonadal hormones were progressively loss throughout the 30 years of follow-up available.
Conclusion
Gonadotrophin-sparing pituitary deficiency is not infrequent in our LEEC cohort. Tempo of hormonal losses suggest that surveillance for steroid and thyroid axes can be stopped after 15 years but surveillance for gonadal axis should continue beyond 20 years.

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P109

Clinical implications of splicing machinery alteration in Pheochromocytomas and Paragangliomas

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Pheochromocytomas and paragangliomas (PPGL) are infrequent neuroendocrine neoplasms, which develop metastases or aggressive behaviour in 25 % patients. They can be classified into three clusters according to their molecular features; nevertheless, these differences may not stratify patients according to their prognosis. The dysregulation of the splicing process has emerged as a novel feature shared by most cancers, which is associated with an aggressive phenotype in several tumours, including NETs, but it has not been explored in PPGL. The purpose of this study was to determine the splicing machinery profile in PPGL, its relationship with clinical/molecular features, and to investigate the functional role of splicing inhibitors in vitro. We investigated the expression of 310 splicing-related genes in a dataset of 196 PPGL and analysed their relationship with clinical features of patients and tumor phenotypes, which was validated using the TCGA dataset. SK-N-AS (WT and *SDHB* knock-down), and PC12 cell lines were used to perform in vitro assays testing the effects of the SF3B1 inhibitor Pladienolide B. Pheochromocytomas and paragangliomas show clearly distinct profiles of splicing machinery components. Interestingly, clear differences were observed among the molecular clusters. Furthermore, the expression levels of certain splicing-related genes were associated to metastasis, aggressiveness, and low survival. The *in vitro* blockade of the splicing process reduced functional parameters of aggressiveness as proliferation, colony formation, migration, and sphere formation. Finally, our findings revealed that the splicing machinery is severely altered in PPGL, which may be associated with key clinical features, and its modulation may improve tumour aggressiveness.

Keywords
pheochromocytoma, paraganglioma, splicing dysregulation, splicing machinery, pladienolide B.

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P110

Should patients with incomplete microscopic resection of papillary thyroid carcinoma be classified as high-risk ones for the recurrence/-persistent disease?

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Introduction
In recent years the growing rate of newly diagnosed papillary tyroid cancers (PTC) has been observed. Nowadays most of PTC are small (mostly $<$2cm in diameter) with no unfavourable patomorphological features, although the cases of incompletely resected PTC can still be encountered. Incomplete tumour resection, regardless of the presence of microscopic (R1) or macroscopic (R2) disease, after operation, is considered as a high-risk factor for PTC recurrence/persistent disease both by American Thyroid Association (ATA) and European Society for Medical Oncology (ESMO) recent guidelines.
Aim
The aim of our study was to assess the relationship between resection margin status (R0 vs R1) and the clinical outcomes (response to therapy, recurrence presence) in Polish patients with PTC.
Materials and Methods
A retrospective analysis of 2674 patients, who were enrolled to the study, from a single tertriary oncologic referential centre, operated between 2000-2021, was performed. From this group 1975 patients were further qulified for study: 1819 who had R0 resection status and were assessed as having low-risk cancer according to ATA guidelines (ATA-LR) and 156 who were treated as high-risk cancer (HR-ATA) only due to incomplete microscopic tumor resection (R1).
Results
In the group with R0 resection the excellent response to therapy, at the end of follow-up, was observed in 1738 (95.55%) patients and indeterminate response was observed in 76 (4.18%) cases. The biochemical incomplete response to therapy, during last follow-up, was detected in 1 (0.05%) patient. Structural incomplete response was stated in 4 cases (0.22%). There were 11 cases of reccurence (definied as diagnosing cancer after achieving so-called ''no evidence of disease'' due to prior treatment) of which 10 (90.91%) were treated succesfully and excellent response was achieved. In total, the risk of recurrence/persistent disease in patients with R0 resection was 5.24% (91/1738). In the group with R1 resection the excellent response to therapy was observed in 139 (89.1%) patients and indeterminate in 11 (7.05%) cases. The biochemical incomplete response to therapy was detected in 3 (1.92%) patient. Structural incomplete response was stated in 3 cases (1.92%). There were 2 cases of reccurence of which none achieved excellent response. In total, the risk of recurrence/persistent disease in patients with R1 resection was 10.9% (17/156).
Conlusions
Due to lower risk of unfavourable outcomes when incomplete microscopic resection is observed in differentiated thyroid cancer the consideration of treating cases with R1 feature as ''intermediate cancer'' for recurrence/persistent disease should be made.

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P111

Body composition of Patients with advanced Gastroenteropancreatic (GEP) Neuroendocrine Neoplasms (NENs) in Spain: Nutrigetne Study

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Introduction / Background
Patients with advanced GEP-NENs often present with metabolic disorders and oncological treatments may increase malnutrition risk as well as alterations on body composition. Several studies have suggested that sarcopenia is independently associated with a worse prognosis in oncological patients. Sarcopenia predicts survival regardless of body weight; moreover, a reduced muscle mass is not only observed in cachectic individuals but also in overweight patients.
Aims
The aim of this study is to describe body composition and to evaluate functionality of patients with advanced GEP NENs in Spain.
Materials and Methods
Cross-sectional study including patients with GEP-NENs at a metastatic/unresectable stage and active oncological treatment. Patients had a complete demographic evaluation, physical examination, anthropometry, bioelectrical impedance, dynamometry, laboratory analysis, and nutritional risk assessment. Malnutrition was defined according to GLIM criteria and sarcopenia according EWGSOP criteria. The study plans to include 400 patients; Accrual is open. Pearson's $\chi 2$ test with α 0.05.
Results
284 patients were included. Median age was 63 years (24-83). The most frequent tumor location was small bowel (44.7%) and pancreas (43%). 94.7% were metastatic, 88.4% grade 1-2 and 83.8% had ECOG 0-1, and 23.6% were functioning. The most common previous/current treatments were somatostatin analogues (89.8%), targeted therapy (29.9%), peptide receptor radionuclide therapy (28.9%) and chemotherapy (19.7%). 50% of the patients were on first line treatment, 23.9% on second line and 26% were on more than two lines. Malnutrition prevalence was 62% ($n=176$) being severe in37.7%($n=107$). Low muscle mass was the most common GLIM phenotypic criteria, present in 139 patients (48.9%), being severe in 25.7%. Mean calf circumference was 34.2(4.8)cm and 36.5(5.5)cm, free fat mass of 41.4(10.6)kg and 56.1(11.8)kg and handgrip strength of 19.2(6.9)kg and 36.3(9.5)kg in females and males respectively. Mean phase angle was 7(9.3)° and 7(8.9)° in females and males respectively. Sarcopenia was present in 22.5%. Patients with malnutrition showed decreased handgrip strength ($P<0.001$).
Conclusions
Malnutrition among patients with advanced GEP-NENs is high, being low muscle mass the most frequent phenotypic criteria in patients with GEP-NENs present in half of the patients. One every five patients with GEP-NENs had sarcopenia.

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P112

The involvement of endocannabinoid system in Multiple Endocrine Neoplasia type 1 (MEN1)

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Background
Multiple endocrine neoplasia of type 1 (MEN1) is a rare heritable endocrine tumor syndrome that results from biallelic inactivation of the MEN1 gene and the loss of menin protein, that was characterized by a susceptibility to the development of multiple endocrine neoplasms within a single patient. The MEN1 gene screening is helpful in the clinical practice for early genetic diagnosis. Unfortunately, the lack of genotype-phenotype correlation doesn't allow to foresee the syndrome's clinical course, consequently, reducing the possibility to develop a personalized diagnostic and therapeutic plan. Recently, it has been reported that menin is capable to suppress the Hedgehog signalling pathway (Hh) MEN1-dependent tumors and its loss might cause the over-activation of this proliferative and oncogenic pathway. Moreover, emerging evidence highlight that Hh pathway and MEN1 tumorigenesis could be under the control of epigenetic mechanisms, including miRNAs. In addition, results obtained over the last years demonstrated that cannabinoids regulate miRNA expression in BV-2 microglial cells and are endogenous conserved inhibitors of the Hedgehog (Hh) pathway. However, no data are currently available on the relationship between the endocannabinoid system (ES), Hh pathway, and miRNAs in MEN1 syndrome.
Materials and methods
First, in silico analyses, using TargetScan, miRanda, and miRNet software, were performed to find the possible binding between miRNAs and different factors involved in the Hh pathway. Next, cell biology analyses were carried out for a preliminary assessment of the ES components expression in different neuroendocrine tumor cells (i.e., insulinomas, gastrinomas, and prolactinomas) derived from MEN1 patients. Finally, we observed the effects of Anandamide (AEA) on insulinoma cells proliferation.
Results and future perspective
In silico analysis indicated the 3' untranslated region (3'UTR) of human Dual specificity tyrosine phosphorylation regulated kinase 2 (DYRK2) mRNA as potential target of miR-24-1-3p, which was deregulated in MEN1 parathyroids and pancreas tumors. Then, PCR analysis showed the presence in the neuroendocrine tumor cells of both receptors (i.e., CNR1, CNR2, GPR55, GPR6, and TRPV1) and enzymes (i.e., FAAH, NAPE e DAGLα) involved in ES. Finally, we observed that treatment with different concentrations of AEA on insulinoma cells led to a decrease in their proliferative capacity, especially with 10 μM and 100nM concentrations. Further studies are needed to validate the latter finding and to subsequently establish the relationship between ES, miRNAs, Hh pathway, and MEN1 tumorigenesis. In conclusion, this project could pave the way for the possible future endocannabinoid-based drug development against MEN1 syndrome.

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In silico neoantigen prediction - a forceful avenue to improve immunotherapy in human adrenocortical carcinoma

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Introduction
Adrenocortical carcinoma (ACC) is one of the most aggressive endocrine malignancies and confers a poor prognosis in advanced stages. Effective treatments are lacking. The results of immune checkpoint inhibition were disappointing with few responders only deriving clinical benefit. For the development of novel immunotherapies such as tumor vaccines and T cell-based treatments, target identification is essential. Tumor-specific mutant

neoantigens that may be recognized by T cells in the context of major histocompatibility complex (MHC) I are promising candidates.
Methods
We performed whole exome-sequencing in 10 ACC samples with matched blood controls. Somatic mutations were identified using an in house bioinformatics pipeline. By coupling POLYSOLVER for HLA typing with netMHCpan, *in silico* binding affinity of tumor-specific neoantigens to MHC was calculated taking into account both peptide and HLA sequence information. Strong binding (SB) was defined as $<0.5\%$ rank, weak binding (WB) as 0.5-1.9% rank and no binding (NB) as $>2.0\%$ rank of all peptides to MHC.
Results
Across 10 ACC patients, we identified 1067 unique somatic mutations (median 49.5, ranging from 15-590), affecting 989 different genes. Binding affinity changed for 414 predicted neoantigens from NB to WB, 80 from NB to SB and 82 from WB to SB. The mutant neoantigen load per patient ranged from 10 to 235 (mean 66.2) and was positively correlated to the total number of non-synonymous single nucleotide variants (R^2 0.8977, 95% CI 0.79-0.99; $P<0.0001$).
Discussion
This is the first study that demonstrates successful *in silico* neoantigen profiling in ACC. Mutant neoantigens were predicted to be present both in ACC with high and low tumor mutational burden. These data will pave the way for *in vitro* validation and hold potential to develop therapeutic cancer vaccines and T cell-based cancer immunotherapy in ACC.

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Hyperandrogenism in menopause: whose fault?

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Background
Hyperandrogenism in postmenopausal women is extremely rare and requires exclusion of malignancy.
Case reports
1. A 65-year-old woman was referred to our Department of Endocrinology for appearance of hirsutism and alopecia for about 2 years. Abdomen-pelvis CT scan showed a 2-cm lesion (45 HU) at the left adrenal gland, confirmed by MRI scan, without loss of signal intensity in opposed-phase sequences. In addition, in the right ovary, a 3-cm lesion with progressive enhancement was found, suspected for malignancy. Hormone assays detected increased levels of adrenal and ovarian androgens (DHEAS 107.7 µg/dl, Delta 4-Androstenedione 401 ng/dl, Testosterone, Te, 5.97 nmol/l), Estradiol (40 pg/ml) and Urinary Free Cortisol (298 mg/24h) with normal to low values of ACTH (14.5 pg/ml) and inappropriately normal for age LH values. She therefore performed a 18F-FDG PET scan, which showed uptake in the left adrenal (SUVmax 6.5) and a focal and inhomogeneous distribution of the tracer in the right ovary (SUVmax 4.1). She then underwent left adrenalectomy, with normalization of adrenal androgen levels but persistence of elevated Te levels post-surgery (8.69 nmol/l). She therefore performed bilateral oophorectomy, with subsequent normalization of Te levels (1.19 nmol/l). Histological examination showed left adrenal adenoma and steroid cell tumor of the right ovary.
2. A 73-year-old woman was referred for clinical hyperandrogenism (alopecia and hirsutism for about 20 years, with worsening in the last 4 years) with increased Te levels (5.5 nmol/l). She performed adrenal-pelvis MRI scan, which found two lesions in both adrenal glands (9 mm in the right and 13 mm in the left), referable to adrenal cortical nodular hyperplasia. In addition, both ovaries were enlarged, but free from lesions. Basal hormone assessment showed a marked increase in serum Te (6.58 nmol/l), 17-OH-Progesterone (2.4 ng/ml) and gonadotropin levels (FSH 76.22 mUI/ml, LH 24.99 mUI/ml). A normal short Synacthen test for 17-OH-Progesterone excluded congenital adrenal hyperplasia, while a prolonged Dexamethasone test for androgens failed to suppress Te levels. Ovarian hyperthecosis was hypothesized. The patient was, thus, addressed for bilateral oophorectomy.

Conclusions
The coexistence of adrenal and ovarian androgen-secreting lesion, although rare, is a possibility and a challenge for the endocrinologist in the differential diagnosis of hyperandrogenism.

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P115

Hand-foot syndrome: a frequent but rarely severe adverse event in patients with thyroid cancer treated with lenvatinib

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Introduction
Hand-foot syndrome (HFS), or palmo-plantar erythrodysplasia, is an adverse event related to lenvatinib therapy. In the clinical trial (SELECT study) HFS was reported in 32% of patients, but only 3% was grade ≥ 3. In real-life studies the frequency was variable: between 8 and 55%.
Patients
We collected clinical and pathological data about 165 patients with thyroid cancer treated with lenvatinib, followed up between 2012 and 2022 at the Endocrinology Unit of the University Hospital of Pisa.
Results
Fortythree out of 165 (26.7%) developed HFS during lenvatinib treatment after a median time of 2.9 months (IQR 1.14-6.79) from the beginning of the treatment. Among these 43 cases of HFS, 24 (55.8%) were classified as grade 1, 16 (37.2%) as grade 2, 3 (7%) as grade 3/4. Because of the HFS, in 2 patients drug dose reduction was required, while in one patient a transient discontinuation of lenvatinib was necessary. All patients were treated with topical therapy. Grade ≥ 3 cases required podiatrist intervention and specific footwear. The comparison between those patients who developed HFS and those who did not developed HFS showed a significant association with age (mean 63 ± 8.97 years vs 66.61 ± 10.14; $P=0.032$) and duration of lenvatinib therapy [median 15.96 months (IQR 8.47-46.72) vs median 12.68 months (IQR 4.48-27.23); $P=0.039$]. No significant association was found concerning sex (females 29.62% vs females 23.75%), presence of distant metastasis (M1), thyroid carcinoma histotype, the starting dose of lenvatinib (mean $21.12 \pm$ 4.79 mg/die vs mean $19.46 \pm$ 6.04 mg/die), and prior treatments (131-I, chemotherapy, external radiotherapy, other multikinase inhibitors).
Conclusions
HFS is a frequent adverse event related to lenvatinib but rarely of grade ≥ 3, such as to require reduction or discontinuation of the drug. In our series, HFS was more frequent in younger patients and those who was using Lenvatinib since more time. Further studies are needed to understand the pathogenesis and risk factors related to the occurrence of HFS.

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P116

Impact of Gender on Treatment Decisions and Outcome in Patients with Neuroendocrine Neoplasms

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Introduction/Background
Gender differences affect the treatment of several diseases in both male and female patients. However, the influence of gender on treatment decisions and outcome in neuroendocrine neoplasms (NENs) has scarcely been investigated.
Aims
Comparison of tumor characteristics, treatment decisions and outcome of patients with NENs, stratified by gender
Material and Methods
Retrospective analysis of the SwissNET cohort involving NENs of gastroenteropancreatic, pulmonal or unknown origin from 07/14 – 09/21. Site of origin, tumor grading, time to first treatment, choice of treatment and overall survival was assessed.
Results
2329 patients were included in the analysis with 54% being male and 46% female patients. No significant difference in site of origin, tumor grading and staging was found between male and female patients. There was also no difference in time of symptoms onset until diagnosis and first treatment intervention. Surgery was performed in 66.3% of male and 71% of the female patients, $P=0.016$. Meanwhile, male patients received more often PRRT (22% vs 19.3%, $P=0.007$) and chemotherapy (15.9% vs 12.7%, $P=0.032$). Despite the similar tumor characteristics, the median overall survival of male patients was significantly lower compared to female patients (Male: 124.8 months, Female: 158.5 months, $P<0.001$). Interestingly, this difference was most pronounced in patients with

lung NENs (Male: 142 months, Female: not reached) and cancer of unknown origin (Male: 18.5 months, Female: 35 months).
Conclusions
Male gender seems to be a risk factor for worse outcome, specifically for lung NENs and NENs of unknown origin. The underlying mechanisms of these findings remain to be established.

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P117

Pivotal phase III COMPOSE trial to compare lutetium (177Lu) edotreotide with best standard of care in patients with well-differentiated aggressive grade 2 and grade 3 gastroenteropancreatic neuroendocrine tumors

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Background
Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) represent an estimated 70% of NETs. GEP-NETs frequently develop metastatic disease with limited treatment options. For well-differentiated high grade 2 and 3 GEP-NETs, current therapies include peptide receptor radionuclide therapy (PRRT), somatostatin analogues, chemotherapy, cytoreduction, and molecular targeted therapies (everolimus, sunitinib). PRRT uses radiolabeled somatostatin analogues to selectively target somatostatin receptor expressing (SSTR+) tumor cells. The radiolabeled somatostatin analogue lutetium (^{177}Lu) edotreotide has shown promising efficacy and a favorable safety profile. Retrospective data in patients with metastatic GEP-NETs treated with two or more lutetium (^{177}Lu) edotreotide cycles demonstrated nearly 30 months progression-free survival (PFS). COMPOSE (NCT04919226), a prospective, randomized, controlled, open-label, multi-center Phase III study, aims to extend therapeutic options for patients with well-differentiated aggressive grade 2 and grade 3, SSTR+, GEP-NETs. Furthermore, functional imaging and genetic profiling analysis as part of COMPOSE plans to guide detection of specific traits in NET patients, to potentially improve treatment and surveillance strategies.
Trial design
COMPOSE evaluates efficacy, safety, and patient-reported outcomes of first- or second-line treatment with lutetium (^{177}Lu) edotreotide PRRT. At least 202 patients with SSTR+ disease will be randomized 1:1 to up to six cycles of lutetium (^{177}Lu) edotreotide, given at 6- to 8-week intervals, or to an active comparator (CAPTEM, FOLFOX or everolimus, according to investigator's choice). PFS, the primary endpoint, will be assessed every 12 weeks until disease progression (RECIST v1.1) or death, whichever occurs earlier. Overall survival, assessed up to 2 years after disease progression, is a secondary outcome. In addition, baseline fluorodeoxyglucose and SSTR positron emission tomography imaging, full exome sequencing and gene expression analysis of tumor histology and longitudinal blood samples will be studied. DNA will be assessed to determine the impact of different types of mutations; mRNA will be assessed to confirm and quantify these assumptions and compare gene expression at different treatment phases. COMPOSE recruitment commenced in September 2021 and comprises of 40 study sites in the United States, Europe, India and Australia.
Conclusion
COMPOSE results are expected to inform about optimal treatment options for patients with well-differentiated aggressive grade 2 and grade 3 SSTR+ GEP-NETs. Moreover, the genetic profiling analysis may assist in developing predictive models that would integrate genetic data with functional and structural imaging, histopathology and phenotype information for implementation into clinical practice.

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Survival, obesity and quality of life after childhood-onset craniopharyngioma: The role of age at diagnosis and hypothalamic damage

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Background
Adamantinomatous craniopharyngiomas (CP) are rare malformational tumors. The association between age at diagnosis and the outcome, clinical presentation and treatment of pediatric CP patients is not clear. The aim of this cohort study was to determine clinical presentation, outcome and quality of life in CP patients diagnosed at different AaD.
Methods
Seven hundred and twenty-two patients diagnosed with CP were recruited 1999-2021 in HIT-Endo, KRANIOPHARYNGEOM 2000/2007/Registry2019 and prospectively observed. AaD was categorized as infants and toddlers (<2y), early childhood (2–<6y), middle childhood (6–<12y) and early adolescence (12–<18y). After median follow-up of 8.4 years, overall and event-free survival (EFS), functional capacity (FMH) and quality of life (QoL) (PEDQOL) were assessed. Multivariable cox regression was applied to compare the survival of three age groups in dependence of HI and HL. Multivariable logistic regression was used to determine potential risk factors for obesity (BMI SDS >3) at last visit.
Results
In this cohort, the prevalence of severe obesity (BMI >3SDS) was 45.4%. No differences regarding surgical approach were determined between the age groups. Lower EFS but better QoL was observed in children with AaD <6y compared to □6y. Reduced functional capacity (FMH) percentiles were associated with increased BMI-SDS at last visit (rho = -0.125, 95% CI [-0.21; -0.04]) and AaD < 2y. Posterior HI and HL are independent risk factors for events (HR = 1.59, 95% CI [1.12;2.26]) and obesity at last visit (OR = 2.94, 95% CI [1.73;5.08]). Patients with posterior HI and HL report worse scores on PEDQOL body image domain.
Conclusions
Severe obesity is a frequent sequela in nearly half of all pediatric CP patients. Diagnosis of CP at an age <6 years, enables patients to adapt earlier to disabilities, but increases the probability of CP relapse. Posterior HI and HL can lead to obesity (BMI SDS >3), which reduces the functional capacity and self-evaluation on body image. Therefore, GTR should be viewed critically.

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Improvement of Lung NET Management through standardized Care – a Swiss nationwide observational Study

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Introduction/ Background
Typical (TC) and atypical carcinoids (AC) are the most common neuroendocrine tumors (NETs) of the lung. Being a rare disease, the management of these tumors varies widely among Swiss centers. The impact of guidelines introduced in 2015 is unknown.
Aims
Comparison of the management of Swiss patients before and after the publication of the expert consensus of the European Neuroendocrine Tumor Society (ENETS) in 2015.
Material and Methods
Retrospective analysis of patients with TC and AC using data from the Swiss NET registry from 2009 to 2021, focusing on diagnostic evaluation and treatment before and after 2016. Survival analysis was performed using the Kaplan Meier method and log-rank test.
Results
Overall 238 patients were included, thereof 75,6% (180) with TC and 24,4% (58) with AC, with 155 patients included before and 83 patients after 2016. An increase in the use of functional imaging was observed, 10,3% (16) before and 22,8% (19) after 2016 respectively, $P<0{,}001$. In histopathological evaluation, the presence of SST2A-receptors was determined more often; 14,8% (23 times) before 2016 and 26,5% (22 times) after, $P<0{,}001$. Concerning the therapeutic approach, higher removal of lymph nodes after 2016 was observed, 53,5% (83) before compared to 78,3% (65) after, $P<0{,}001$. No difference in mortality was seen before and after 2016. Generally, median overall survival for patients with

AC was significantly shorter with 89,5 months compared to 156,9 months for patients with TC, $P<0{,}001$.
Conclusions
The ENETS guideline recommendations have ameliorated the management of TC and AC, however there is still room for further standardization and improvement.
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P120

Risk of Bilateral Testicular Germ cell Tumors: a single center long-term experience
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Background
Bilateral testicular germ cell tumors (B-TCGT) are reported as rare findings (incidence 1-8%) and can be distinguish in synchronous (sB-TCGT) (recurrence within 3 months) and metachronous (mB-TCGT) (recurrence after 3 months). Risk factors of relapse are still underexplored. The aim of our study was to identify clinical, biochemical and radiological risk factors for the onset of a second tumor in a wide cohort of TGCT patients.
Materials and Methods
This is a retrospective, monocentric case-control study including TGCT-patients who performed regular ultrasound (US) follow-up at the *TestisUnit* of Policlinico Umberto I, Rome, Italy, from 2006 to 2021. Testicular US, post-orchiectomy hormones and semen analysis were all performed in our institution. Data from serum tumor markers (STM), histological examination, post-orchiectomy treatments and follow-up time were recorded. Patients with mB-TGCTs were compared with unilateral TGCT patients with a follow-up greater than the median time-to-onset of the second tumor, which represented our control group (u-TGCT). The statistical analysis was carried out with non-parametric tests.
Results
The final population included 243 patients with TGCT: 158 (65%) with seminoma, 85 (35%) with non-seminoma. Among B-TGCT, 11 were sB-TGCT and 36 mB-TGCT. Among mB-TGCT, the median time-to-onset of the second tumor was 56.5 months [IQR 28;138 (range 8-211)]. u-TGCT group included 100 patients. mB-TGCT compared to u-TGCT showed a residual testicle with lower volume [10.4mL (8.9;13) vs. 16.3mL (12.0;19.1), $P<0.001$], more inhomogeneous echotexture [27/36 (75%) vs 50/100 (50%), $P=0.003$] and testicular microlithiasis (TML) [28/36 (77.7%) vs 24/100 (24%), $P<0.001$]. mB-TGCT presented higher gonadotropin values [FSH 12.1 mIU/ml (6.0;34.5) vs 5.9 mIU/ml (2.8;9.3), $P=0.003$; LH 6.5 mIU/ml (2.8;13.4) vs 3.4 mIU/ml (1.9;5.2), $P=0.014$] with similar testosterone levels ($P=0.862$) and lower sperm concentration [$6x10^6$/ml (0.1-32) vs $21x10^6$/ml (5.7-48), $P=0.045$]. No differences were found in the two groups for clinical history, histological features, STM and post-orchiectomy treatments. Kaplan-Meier curves confirmed that patients with contralateral testicular volume <12 mL ($P=0.023$), inhomogeneous echotexture ($P=0.011$) and TML ($P<0.001$) had a higher cumulative risk of development of a second tumor. Logistic regression analysis showed that the presence of TML was the best independent predictor (OR 13.992, 95%CI:1.96-99.897, $P=0.009$).
Conclusions
B-TCGT is not such a rare event. Patients with a low volume surviving testicle, with inhomogeneous echotexture or TML have a cumulative increased risk of developing a second tumor. US follow-up is mandatory and a complete morpho-functional evaluation of the contralateral testis is essential to set up a personalized program.
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Thymic Neuroendocrine Tumor Presenting as Cushing's Syndrome
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Introduction
Cushing's syndrome (CS) is a rare disease with incidence estimated 2-4 cases per million inhabitants per year. ACTH-dependent forms comprise up to 80% of all cases, of which 80% are central and 20% are ectopic, paraneoplastic forms of ACTH-dependent CS. Thymic neuroendocrine tumors (NET) are accounting for 0,4 - 3% of all NET's with incidence of 0.02/100 000 inhabitants/year. Up to one third of them are hormonally active (secrete adrenocorticotropic hormone - ACTH, antidiuretic hormone, growth hormone releasing hormone and other hormones).
Clinical case report
A 39-year-old man presented with a rapid development of CS. CS was only partially expressed due to its relatively short history - discrete Cushingoid facies, hyperpigmentation, hypertension, sleep disorders, decreased libido, depression and also complaints of intermittent retrosternal pressure and mild cough. Examination proved highly active ACTH-dependent paraneoplastic hypercortisolism (ACTH 247 ng/l, free urinary cortisol 3220 nmol/day, unsuppressed cortisol in 1mg dexamethasone test: 1110 nmol/l) with hypokalemia and glucose intolerance. CT showed an anterior mediastinum tumor 69x47x64mm. Tumor was resected. Histopathology revealed a thymic atypical carcinoid - neuroendocrine tumor grade 2, however, a resection margin was positive for tumor cells. Postoperatively, the symptoms of hypercortisolism vanished and a central hypocortisolism was proved. As a postoperative OctreoScan examination was negative, no adjuvant therapy was started. Thirteen months after the surgery, laboratory markers suggested recurrence of hypercortisolism. Two tumor masses close to the pulmonary veins found on imaging were considered inoperable. Therefore, cyber knife irradiation was applied, and lanreotide and everolimus were initiated. The effect was insufficient and new metastases appeared in spine, lymphatic nodes, myocard and lungs. Palliative chemotherapy was started - using dacarbazine, subsequently capecitabine and oxaliplatin. What is more, hypercortisolism was not sufficiently suppressed by pharmacotherapy (ketoconazole, metyrapone), which necessitated palliative bilateral adrenalectomy. Later, due to metastatic disease, the patient suffered from malignant pericardial and pleural effusions, both of which required repetitive drainage (in spite of application of cisplatin for pericardial one), and obstructive jaundice caused by tumorous infiltration of gall bladder and pancreas. He died 42 months after the first surgery.
Conclusion
Thymic neuroendocrine tumors are very rare. One third of them manifests itself by paraneoplastic secretion of hormones. Finding the origin of hormone production in ectopic CS can be very challenging but is pivotal for the causal resection of the tumor. The other therapy options include somatostatin analogues, everolimus or chemotherapy.
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Early calcitonin levels in medullary thyroid carcinoma: prognostic role in patients without distant metastases at diagnosis
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Introduction
Calcitonin (CT) is the most specific marker for medullary thyroid carcinoma (MTC), thus, even low detectable values can conceal persistent disease. Current guidelines suggest performing an early CT evaluation three months after surgery. However, this timing may be too premature to evaluate the CT nadir, since different isoforms or aggregates from tumour deposits may persist in the bloodstream and require additional time to be cleared. The present study aimed to explore the prognostic role of pre-operative and *early* CT levels, in MTC patients without distant metastases at diagnosis.
Methods
A retrospective cohort of patients suffering from medullary thyroid carcinoma without distant metastases at diagnosis was considered ($n=55$). The final disease status, i.e. *complete response* (undetectable CT levels and negative radiological assessments) or *persistent disease* (detectable CT levels and/or positive radiological assessments), was deduced from the last available follow-up. Pre-operative and *early* CT levels (i.e. six months after surgery) have been correlated to several clinical and histological features, according to the final disease status.
Results
Persistent disease patients ($n=27$) showed higher pre- and *early* CT values ($P=0.028$ and $P<0.001$, respectively), compared to *complete response* sub-cohort ($n=28$). After a median follow-up of 39.2 months [16.3-83.7], six patients died, while 12 patients (21%) developed distant metastases. A pre-surgical CT value of 284 pg/ml

showed a sensitivity of 69.2% and a specificity of 68.0 % in predicting the final outcome (AUC= 0.679, CI95:0.525-0.833, $P=0.028$). In a similar ROC model, the lowest detectable CT value at six months follow-up (i.e. 0.7 pg/ml) of the present cohort was able to predict the final outcome with a sensitivity and a specificity of 95.8 % and 80.0%, respectively (AUC= 0.958, CI95: 0.900-1.0, $P<0.001$). In fact, only five patients (9.1% of the population) with a final *complete response* status showed *early* detectable CT values. The cox-regression model shows that early detectable CT levels increase up to 18-fold the risk of persistent disease, independently from tumour size and pre-operative calcitonin levels (O $r=18.53$, CI95%: 2.25-152.8, $P=0.006$). Of note, when considering only patients who finally developed distant metastasis, ROC curve analysis shows that an *early* CT level ≥ 16 pg/ml predicts the final disease status with a sensitivity of 89% and a specificity of 82% (AUC=0.911, CI95%: 0.819-1000, $P<0.001$).

Conclusions

CT levels six months after surgery are an easy and effective predictor of persistent disease for medullary thyroid carcinoma without distant metastases at diagnosis.

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Urea for treatment of hyponatremia in SIADH – an old treatment for a current problem

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Introduction

There are several endocrine causes of hyponatremia. SIADH is perhaps the most challenging, as patients do not always respond to initial correction measures and pharmacological treatment options are scarce. Urea is a viable option, but not commonly used.

Methods

Analysis of patients with SIADH-induced hyponatremia (<135mEq/l) treated with urea *per os* in the Portuguese Institute of Oncology of Porto between August 2021 and October 2021.

Results

Seventeen patients were included, with median age of 61 (19,5) years. In 15 patients, SIADH had a neoplastic etiology, mostly in the context of small cell lung carcinoma, and in 2, several factors, including pharmacological ones, contributed to the syndrome. Serum sodium nadir was 117 (11) mEq/l. Most patients received treatment with 0,9% saline, hypertonic saline, water restriction and/or increased protein/salt consumption before starting urea. They presented a pre-therapeutic sodium of 123 (5,5) mEq/l, plasmatic and urinary osmolality of $261\pm9,74$ and 558 (263,5) mOsm/kg, respectively, and urinary sodium of 97 (102). Urea was started orally at a dose of 10mg bid. Fourteen out of 17 patients were reevaluated 48-72h later, showing a statistically significant rise in plasma sodium [127 (4,5) ($P=0,009$)]. Patients continued treatment for a median of 96 (196) days, and plasma sodium continued to improve until their last bloodwork [sodium 134 (7) mEq/l; $P<0,001$)]. There was no clinically relevant change in renal function [(pre and post treatment creatinine $0,55\pm0,17$ vs. $0,65\pm0,2$, respectively ($P=0,007$)], and no other adverse effects were recorded.

Conclusions

Urea appears to be a safe and effective treatment for patients with SIADH-induced hyponatremia refractory to the usual initial correction measures.

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Exploring the interplay of RNA methylation and alternative splicing machineries in lung carcinoids

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Lung carcinoids are slow-proliferating neuroendocrine neoplasms commonly showing low mutational burden but a high heterogeneity and difficult clinical management. Despite valuable advances in their molecular characterization, some aspects remain still unknown. Recent studies have shown that alternative splicing is severely dysregulated in lung carcinoids, where it could promote tumoral features. In contrast, the role of some molecular systems closely related to splicing and other RNA processing mechanisms has been poorly explored in these rare tumors. An emerging example of this is the machinery that regulates the methylation of RNA (N6-methyladenosine or m6A), the most usual internal modification of RNA, which is largely understudied in this pathology. We hypothesized that m6A processing machinery may be altered in lung carcinoids and linked to splicing dysregulation, thus RNA metabolism would be severely modified in these tumors. Our main aim was to identify alterations in the m6A process coupled to RNA splicing changes that may interfere with lung carcinoid development and aggressiveness. To this end, we have carried out a pilot analysis on 16 atypical carcinoids, and, through biocomputational analyses, we have assessed the expression of 13 m6A regulators, exploring their putative associations with clinical features and splicing alterations. Remarkably, we observed a clear relationship between the expression levels of several m6A readers and patient survival, highlighting the relevance of these factors. Interestingly, we found a strong link between abnormal m6A-related gene expression and cellular functions and pathways associated with carcinoids tumorigenesis, development, and aggressiveness features. Among them, the more remarkable ones were related to key metabolic pathways, including cellular adhesion, ionic transport, and tumor-related features, such as proliferation, differentiation, and increased sensitivity to growth factors. Altogether, our preliminary results suggest that lung carcinoids also possess another level of RNA processing dysregulation involving m6A alteration, which would be linked to tumor development and aggressiveness and may be useful in the future to improve the clinical management of this disease.

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P125

Audit of Incidence and Management Practices of Endocrinopathies due to Immunotherapy and introducing a new locally adapted Guidelines for better monitoring and Management

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Background

Immune related adverse events (iRAEs) of the endocrine system are commonly recognised in Checkpoint Inhibitor (CTLA-4 and PD-1 inhibitors) Therapy. Clinically, endocrinopathies can present with symptoms of hormone deficiency, hormone excess or both (in the same or different glands).

Aim

Audit of Incidence and Management (detection, investigation, referral and management) practices of Endocrinopathies due to Immunotherapy in Oncology department for the duration of six months January-June 2019. We aimed to improve management of endocrinopathies through peer led education and new locally adapted guidelines.

Methods

A retrospective anonymised audit of all patients receiving immunotherapy was done. Data sources included outpatient clinic letters, electronic prescriptions, biochemistry results and multidisciplinary team meeting summaries. Analysis of quantitative data was in percentages and proportions. The detection, investigation, referral and management was assessed on a two point criteria stating adequate or inadequate /appropriate or inappropriate taking UK Oncology Nursing Society (UKONS) Endocrinopathies with Immune Check Point Inhibitors (ICPi) Guidelines as standard. Thereafter with multidisciplinary input from Endocrinology team, a locally adapted new guidelines were written and implemented. The process was re-audited and using the two point assessment and the results will be available for presentation at the conference. The knowledge attitude and practice of doctors in oncology was also assessed with a 10 question questionnaire.

Results

Total number of patients receiving immunotherapy, ipilumab, nivolumab, atezolizumab and pembrolizumab alone or in combination were 101. Total number of patients with endocrinopathies either single or multiple were 37. Total number of endocrinopathies detected(symptomatic/asymptomatic) were 50. Total Incidence of endocrinopathies was found to be 36.6%. Thyroid disorders detected were 16/50(32%), hypoglycemia-2/50(4%), diabetes mellitus(DKA)-1/50(2%).) Hypocortisolism(Biochemical asymptomatic + symptomatic) was 6/50(12%).

Symptomatic hypocortisolism was 5/50(10%) and low testosterone was found in 2/50(4%). Endocrinopathies were detected in first line therapy in 17/37(45%) and in second line therapy in 20/37(54%). The endocrinopathies were distributed amongst cancer sites as lung -29, melanoma-2, colon-2, renal-2, hypopharynx-1, Transitional cell carcinoma-1. The maximum number of endocrine aberrations were found between 3weeks-3months-29/37(78%). The process was re-audited after educational sessions and measurable improvement was achieved in clinical practise.

Conclusions

Total Incidence of endocrinopathies was found to be 36.6%. Most of the management was by individual teams and there was knowledge gap and co ordination identified amongst doctors managing these patients since immunotherapy a new and developing area of practice. KAP questionnaire was used to assess the knowledge gap amongst staff members. Shared learning and multidisciplinary approach can go a long way in management of endocrine side-effects of these novel therapies.

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P126

Carcinoembryonic antigen role in the assessment of neuroendocrine tumors

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Background

The importance of carcinoembryonic antigen (CEA) assessment in the evaluation of medullary thyroid carcinoma is well known. The role of CEA in the assessment of other neuroendocrine tumors (NET) is not clear. We aimed to evaluate a possible correlation between CEA measurements and the aggressivity of NETs.

Methods

We evaluated 56 (36 women) NETs followed in a tertiary center (23 gastrointestinal, 12 pancreatic, 10 pulmonary, 7 without primary tumor localization, 1 urinary bladder and 3 neuroendocrine carcinomas (NEC)). We evaluated a possible correlation with the CEA measurements (absolute values and dichotomic values, larger than the upper normal cutoff value, UNV) and ki67% values, type of NET, the presence of metastases, hepatic or all other types and newly imagistic evaluation suggestive of progressive metastatic disease. All CEA measurements were done using the same technique. Patients with medullary thyroid carcinoma were excluded.

Results

Three patients (5.35%) had values 10 times higher than the UNV, 23 patients (41%) had levels above UNV. Ki67% values were available only for 45 patients, no correlation was found between ki67% and CEA values, correlation coefficient -0.03, $P=0.07$. Also, we didn't find a correlation between abnormal CEA values and the presence of metastatic disease other than hepatic (23 patients), hepatic metastasis (18 patients), gastrointestinal type of NET and newly diagnosed progressive disease (13 patients), with correlation coefficients between 0.13-0.2, p>0.05. The newly diagnosed progressive disease was mainly observed on hepatic metastases. Thirty-eight patients were currently on somatostatin analog (SSA) treatment, no correlation being found between CEA values and the presence SSA treatment (0.12, $P=0.36$).

Conclusion

Data presented does not support a role of CEA in the algorithm assessment of NETs. In the same time, a large number of patients had abnormal values, raising the question of a possible importance of CEA evaluations in this patients, further studies with higher number of patients and correlation with other neuroendocrine markers are warranted.

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Severe ectopic Cushing syndrome in a transgender male with metastatic gastrinoma and adrenal tumor - a case report

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Background

Gastrinoma is a functional neuroendocrine neoplasm (NEN) most commonly located in the duodenum (70%) and the pancreas (25%). The initial confirmation of NEN's secretion profile does not exclude the possibility of a new hormonal activity of the tumor occurring in the course of the disease. Ectopic Cushing syndrome has been described in up to 5% of gastrinoma cases and hypercortisolemia may worsen the patient's prognosis.

Case presentation

A 38-year-old transgender male with advanced metastatic functional PanNEN - gastrinoma was admitted to the Department of Endocrinology due to new symptoms and signs of severe ACTH-dependent hypercortisolemia. The patient's medical history included non-functional adrenal adenoma and chronic gender-affirming hormone treatment with testosterone after the female-to-male surgical intervention at the age of 28 years. Two years before the admission an advanced pancreatic gastrinoma with liver metastases (NET G2, with Ki-67 4-5%) was diagnosed. The patient was disqualified from surgical intervention and the disease was initially managed with somatostatin receptor ligand. Later he was shortly treated with everolimus but it was ceased due to drug-induced interstitial pneumonia. After the diagnosis of ACTH-dependent ectopic hypercortisolemia the patient was qualified for bilateral adrenalectomy after preoperative treatment with metyrapone. Finally, the patient underwent a resection of the left adrenal gland with the tumor, as the right adrenal was surgically inaccessible. Surprisingly, that resulted in a significant decrease in ACTH and cortisol levels leading to clinical remission of Cushing syndrome. Pathology report revealed an adenoma of the adrenal cortex with positive ACTH staining. The result of the simultaneous liver lesion biopsy confirmed a metastatic NEN G2 with positive ACTH immunostaining as well. Subsequently, due to progression of liver metastases in CT and somatostatin receptor scintigraphy, and further increase in gastrin and chromogranin A levels, the patient was qualified for a temozolomide and capecitabine chemotherapy. Although the therapy was discontinued after 4 courses, due to life-threatening anaemia, the patient's NEN is stable and normalisation of ACTH and cortisol levels persists after a one year follow-up.

Conclusion

We present a rare case of the ectopic Cushing's syndrome complicating metastatic gastrinoma. Hypercortisolemia significantly worsens the prognosis of patients with NEN, thus a multimodal approach might be needed, as in presented case. We found it very unusual that the remission of ACTH-dependent hypercortisolemia was noted after removal of one adrenal gland with previously non-functioning adenoma. Furthermore, it is interesting if the gender-affirming hormone treatment influence the neuroendocrine tumor development and progression.

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P379

Association between diabetes mellitus and reduced efficacy of pembrolizumab in non-small cell lung cancer

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Introduction

Type 2 diabetes mellitus (T2DM) and cancer commonly occur together, either because of direct association or merely as both diseases are common among the elderly. The presence of either T2DM itself, or its treatment may affect cancer progression outcomes and response to cancer therapy. Immune-checkpoint inhibitors (ICIs) have become the cornerstone of treatment of several malignancies, including non-small cell lung cancer (NSCLC). As T2DM has been shown to suppress activity of the immune system, we hypothesized that it will impair the activity of ICIs.

Methods

Medical records of all consecutive patients with advanced NSCLC, treated with first-line pembrolizumab either alone or in combination with chemotherapy at Tel Aviv Medical Center (TLVMC) were reviewed. Data on a similar group of patients was extracted from the computerized data of a large Israeli HMO, from Maccabi Healthcare Services (MHS), with over 2.5- million-member.

Results

Two hundred and three eligible NSCLC patients were identified, 51 of them (25%) had T2DM. Compared to patients without DM, patients with DM had a significantly shorter median progression-free survival (PFS; 5.9 vs. 7.1 months,

$P=0.004$) and overall survival (OS; 12 vs. 21 months, $P=0.006$). The differences in OS were significantly more pronounced for patients being treated with pembrolizumab as single agent (12 vs. 27 months, for DM vs. Non-DM, $P=0.03$) but was of borderline significance for those receiving immunotherapy and chemotherapy (14.3 vs. 19.4 months, for DM vs. Non-DM, $P=0.06$). Multivariate analysis indicated DM as an independent risk factor for lower PFS (HR 1.67, 95% CI 1.11−2.50, $P=0.01$) and lower OS (HR 1.73, 95% CI 1.09−2.76, $P=0.02$). A cohort of 452 metastatic NSCLC patients was identified at MHS database. Similarly to the TLVMC cohort, shorter time on treatment was noted for DM compared to non-DM patients, with only 19.6% of patients remaining on treatment at 12 months compared to 31.7% of the non-diabetic patients ($P=0.025$).

Conclusions

These data indicate an adverse effect of T2DM on the efficacy of pembrolizumab in patients with advanced NSCLC. While additional studies are required to better define this association, it is possible that our observation is relevant to other malignancies, as well as other types of ICIs.

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P380

Treatment of childhood-onset craniopharyngioma patients using proton beam therapy vs photon-based radiation therapy in the prospective Kraniopharyngeom 2007 trial

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Background

Proton beam therapy (PBT) compared to photon-based radiotherapy (XRT) offers the benefit to administer lower radiation doses to critical organs thereby possibly minimizing the risk of sequelae in patients with residual craniopharyngiomas (CP) after hypothalamus-sparing surgery. The validation in large CP patient cohorts is still pending.

Methods

Of 290 childhood-onset CP patients included 2007-2019 in the prospective multicenter trial Kraniopharyngeom 2007, 99 (34%) received external RT (65% PBT, 35% XRT). Outcome was compared between the different groups in terms of overall (OS) and event-free survival (EFS), quality of life (QoL using PEDQOL), functional capacity (FMH), and auxological data (BMI and height SDS) one, three and five years after irradiation/CP diagnosis.

Results

PBT became the predominant irradiation technique during the study period (used in 23% and 77% of all irradiated patients registered within the first and second half of the enrollment period, respectively). PBT as well as XRT were associated with high ($P<0.001$) EFS (PBT: 0.917 ± 0.040; XRT: 0.940 ± 0.041) compared to non-RT (EFS: 0.669 ± 0.044). OS was similar in all groups. No differences between PBT, XRT and non-RT CP patients concerning functional capacity and anthropometric parameters (height SDS, BMI SDS) have been obtained. Only in the PEDQOL domain "physical function", proxy-assessed QoL was lower one year after PBT when compared to XRT treated and non-irradiated CP patients. PBT is similar efficient in preventing relapses in childhood-onset CP patients. During follow-up, clinically relevant differences between PBT and XRT in terms of QoL, functional capacity and degree of obesity as a marker of hypothalamic syndrome were not detectable.

Conclusions

While PBT is increasingly applied, studies on larger CP cohorts with longer follow-up after RT are warranted to analyze, whether it can prevent sequelae such as hypothalamic syndrome and severe obesity compared to XRT.

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P381

Gender related differences in patients with carcinoid syndrome: new insights from a multicenter retrospective study

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The incidence of Neuroendocrine Neoplasm (NEN) and related carcinoid syndrome (CS) increased markedly in recent decades, and women appear to be more at risk than men. As per other tumors, gender may be relevant in influencing the clinical and prognostic characteristics. Unfortunately, there are no studies designed to answer this question in the literature. The present multicentric study was designed to evaluated gender differences, if any, in clinical presentation and outcomes of CS. For this purpose, 144 patients affected by CS were enrolled from 18 Italian high-volume centers following the Neuroendocrine Tumors, Innovation in Knowledge and Education (NIKE) project. Clinical characteristics and treatment were collected. Outcomes were evaluated by progression free survival (PFS) and disease specific survival (DSS). The 144 patients diagnosed were 90 (62.5%) men and 54 (37.5%) women. Age at CS diagnosis was no different between the two sexes (median age 61 years, range 26-83, in men and 60 years, range 23-84, in women, $P=0.28$). No differences were observed in the site of the primary NEN, with NEN of the intestinal tract being more prevalent in both sexes (80% and 77.8% in men and women, respectively; $P=0.74$). Patients of both genders differed in clinical manifestations for the occurrence of abdominal pain (53.3% vs 70.4%, $P=0.044$) and tachycardia (6.7% vs 31.5%, $P=0.001$), that were significantly more often found in women, and for the presence of lymph node metastases at CS diagnosis, that was higher in men than in women (80% vs 64.8%; $P=0.04$). Moreover, considering comorbidities and risk factors according to gender, men were more frequently smokers (37.2%) and alcohol drinkers (17.8%) than women (9.5%, $P=0.002$, and 3.7%, $P=0.004$, respectively). Women did not suffer from cardiovascular disease compared to men (0 vs 12.2%, $P=0.0008$). No significant differences emerged in treatment response, prognosis, and overall survival. However, men presented a slightly trend to a shorter PFS (median PFS of 24 months, range 17.1-30.9) than women (PFS 32 months, range 16.7-47.3; $P=0.34$). This study is the first designed to analyze the impact of the gender on CS. The preliminary analysis showed that, in Italy, the prevalence of CS is higher among men (62.5%), unlike the literature. We found that the clinical presentation of CS was different between the two genders, but no clear differences emerged in outcomes of treatment and survival. The characterization and evaluation of the clinical impact of gender-related differences in CS could improve the treatment and the prognosis.

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P382

Decision making, patient involvement and a rare form of thyroid cancer

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In 2022, a 63 year old woman was referred for assessment of a six month history of gastro-oesophageal reflux symptoms and dysphagia. Upper gastrointestinal (GI) endoscopy was normal apart from mild reflux oesophagitis. A computerized tomography (CT) scan demonstrated a 2 cm nodule medial to the caudate lobe of the liver, a 1.5 cm nodule in the right lung base and two further sub cm nodules in the right lung lobe. In terms of background, the patient had a benign breast lump under surveillance and she had undergone a right sided salpingo-oophorectomy in 2008. Following discussion in the upper GI multi-disciplinary team (MDT) meeting she was referred for biopsies of lung nodule and caudate lobe lesion. The paravertebral biopsy of lung nodule was non-diagnostic and an endoscopic biopsy of caudate lobe lesion was suggestive of metastatic thyroid carcinoma (TTF-1 and

thyroglobulin immunostain positive). FDG and DOTATATE positron emission tomography (PET) scans showed no evidence of uptake in thyroid gland but there was uptake in the lung node and in the nodule medial to the caudate lobe. Serum thyroglobulin was 43.1 ug/l with negative anti-thyroglobulin antibody. Thyroid ultrasound showed a 6 x 8 mm exophytic (BTA class U2 i.e. benign) nodule, FNAC confirmed benign cytology (Thy2). Her case was discussed in our central thyroid cancer MDT meeting where it was suggested to review histopathology of the right sided ovary and tube from 2008. This confirmed a large cystic teratoma (weighing 1368 gm) with well-formed thyroid tissue of fetal origin which showed thyroglobulin and TTF1 marker positivity on immunohistochemistry. The patient has undergone total macroscopic removal of the thoracic metastasis and laparoscopic excision of the nodule medial to the caudate lobe of the liver. Histopathology of these samples was similar to the previous atypical thyroid lesion within the mature teratoma of the right ovary, consistent with a diagnosis of metastatic struma ovarii. Although the metastatic disease has progressed slowly, after careful consideration the patient will have thyroidectomy to facilitate radioiodine treatment with a proposed dose of 3.7 GBq. Struma ovarii is a rare ovarian germ cell tumour and comprises only 1.4-2.7% of ovarian tumours. 5-15% of teratomas contain thyroid tissue. The vast majority of struma ovarii are benign, with malignant disease found in less than 5-6% of cases. As struma ovarii is a rare tumour, there is an absence of consensus and guidelines on the management of metastatic disease.

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P383

MiR-191-5p represents a potential personalized diagnostic and therapeutic tool for PCa patients, especially in obesity conditions

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Prostate cancer (PCa) is one of the most common causes of cancer-related deaths in men worldwide. Therefore, more specific non-invasive diagnostic biomarkers with potential therapeutic use are urgently needed. As miRNAs have been proposed as promising elements for the identification of novel diagnostic and therapeutic tools for different pathologies, including different cancer types, we investigated herein the miRNA landscape in PCa patients and explored their putative diagnostic/therapeutic utility. Specifically, the miRNome of plasma samples from healthy ($n=18$) and PCa patients ($n=19$) was initially determined using an Affymetrix-miRNA array (discovery-cohort). The main changes were validated in an independent and ample validation-cohort [$n=202$: healthy ($n=91$) and PCa patients ($n=111$] by quantitative real-time PCR. Additionally, *in silico* and *in vitro* assays in normal (RWPE-1 and PNT-2) and tumor (LNCaP, DU145, and PC-3) prostate cell lines were performed. Results from the discovery-cohort revealed that the expression of 104 miRNAs was significantly altered ($P<0.01$) in plasma samples from PCa patients vs. healthy controls. Of note, 6 of these miRNAs also exhibited a significant ROC curve to distinguish between healthy and PCa patients with an AUC=1. The analyses in the validation-cohort demonstrated that miR-191-5p was one of the most profoundly altered miRNAs in PCa ($P<0.0001$) exhibiting an AUC=0.67. Remarkably, miR-191-5p significantly outperformed the ability of prostate-specific antigen (PSA) to distinguish between control and PCa patients, especially in the "grey zone", which represents the range where PSA levels are less accurate to diagnose PCa. Interestingly, the diagnostic capacity of miR-191-5p was even higher in obese patients (BMI>30). Furthermore, we found that miR-191-5p levels were also dysregulated in PCa cells (vs. non-tumor cells). Moreover, *in vitro* overexpression of miR-191-5p significantly decreased cell proliferation and migration in LNCaP, DU145, and PC-3 PCa cells line. An *in silico* approach using diverse bioinformatics tools was performed to discriminate possible targets that may be regulated by miR-191-5p, finding 13 oncogenic targets, which were further explored in response to mimic overexpression. Of all the targets evaluated, *TMOD2*,a migration-related gene in PCa, was the most consistently decreased, whose levels were also confirmed to be modulated by miR-191-5p. Altogether, our data demonstrate that miR-191-5p might represent a novel and useful personalized diagnostic biomarker in PCa, especially in patients with obesity, as well as a potential therapeutic tool in PCa.

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P384

Impact of SSTR PET/CT imaging on the follow-up of pancreatic NET in MEN1

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Introduction

In multiple endocrine neoplasia 1 (MEN1), the decreased life expectancy is related especially to pancreatic neuroendocrine tumors (panNETs). Timely diagnosis of potentially aggressive panNETs is the cornerstone of the follow-up in MEN1. Somatostatin receptor positron emission tomography (SSTR PET/CT) has a high accuracy in the detection of neuroendocrine tumors. The role of this imaging modality in early diagnosis and follow-up of MEN1-related panNETs is unclear.

Patients and methods

We compared SSTR PET/CT and conventional imaging in 58 patients with MEN1 (median age 40 (range 16–72) years) in Helsinki University Hospital, Helsinki, Finland and in Turku University Hospital, Turku, Finland. SSTR PET/CT was used either as a screening tool in patients without pancreatic NET or in the follow-up of known panNETs. SSTR PET/CT and matched magnetic resonance imaging (88%) or computed tomography (12%) images (median difference between images 3.0 months, IQR 1.2-7.8) were blindly analyzed by two experts. We also assessed the impact of SSTR PET/CT on the management of MEN1 patients during a median follow-up of 46 months.

Results

SSTR PET/CT detected 1.57 ($\pm$2.19) more panNETs per patients than conventional imaging. Significantly more lesions were found in the entire pancreas ($P<0.001$), locating particularly in the head ($P<0.001$) and in the body-tail ($P=0.001$) regions. SSTR PET/CT detected lymph node metastases not identified on conventional imaging in four patients (three abdominal and one mediastinal metastases). There was no statistically significant difference in the amount of suspected hepatic lesions (13 vs 23, $P=0.54$). The SSTR PET/CT changed the management of 27/58 (47%) patients: 7/58 (12%) were referred for surgery, 5/58 (9%) received systemic treatment, and in others the follow-up was intensified. In 15/25 (60%) patients with either no previous panNET ($n=22$) or in remission after surgery ($n=3$), SSTR PET/CT identified a panNET ($n=14$) or recurrence ($n=1$). In eight patients, SSTR PET/CT revealed a panNET not immediately visible on conventional imaging. During a median follow-up of 47 months, three became visible on conventional imaging, but none required intervention. When SSTR PET/CT was negative, no panNETs were identified on conventional imaging during the 38 months of follow-up.

Conclusions

SSTR PET/CT has high accuracy in the detection of MEN1-related panNETs and changes the disease management in nearly half of the MEN1 patients.

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P385

Characterization of telomerase/shelterin system in endocrine intracranial tumors at clinical, transcriptomic, and functional levels

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Intracranial tumors (IT) comprise a heterogenous group of neoplasias (e.g., pituitary/brain tumors and craniopharyngiomas), characterized by difficult diagnosis based on MRI, challenging prognostic predictors and lack of effective therapeutic strategies. In addition, these tumors are usually associated with neurological disorders and severe comorbidities (e.g., those associated with Cushing syndrome, Acromegaly, etc.), worsening the quality life of patients. In this context, several elements of the telomerase/shelterin system, a macromolecular machinery responsible for maintenance of telomers and genomic stability, have been suggested to exert an important role in different endocrine IT (i.e., *TERC* in pituitary tumors, *TERT* promoter in craniopharyngiomas, and *TRF1* in glioblastomas). However, the information about the presence, clinical relevance and potential functional role of the telomerase/shelterin system is still quite limited, fragmentary, and unclear in IT. Therefore, our aim was to extensively characterize the expression levels and clinical/functional relevance of the components of this system in endocrine IT. To that end, expression levels of 17 telomerase/shelterin components were analysed by microarray technology based on qPCR-methodology in different cohorts of IT *vs*. control samples: 1) Pituitary [10 Normal Pituitary (NPs) *vs*. 83 Non-Functioning Pituitary Tumors (NFPTs), 50 GHomas, 19 ACTHomas and 6 PRLomas samples], 2) Brain [7 Normal Brain (NBs) *vs*. 69 brain tumor samples], and 3) 60 Craniopharyngioma *vs*. NP/NB samples. Moreover, several bioinformatic analyses (PLSDA/heatmap/k-means clusterization) with molecular/clinical features, and different functional approaches [e.g., treatment with etoposide (telomerase inhibitor) in selected primary derived cell-cultures and cell line models] were performed. Results revealed an alteration of telomerase expression levels in brain-tumor *vs*. NB samples (e.g., TREF2IP and 4 splicing-variants of *TERT* gene were found to be downregulated in tumor samples, having a diagnostic/prognostic potential). Dysregulation of the telomerase/shelterin system was also observed in different pituitary-tumors *vs*. NPs, being some of these changes common across pathologies (i.e., TERF2, TREF2IP, and TINF2). Interestingly, two different subtypes in NFPTs and GHomas could be identified based on their telomerase/shelterin component profile reinforcing the heterogeneity of pituitary-tumors. A clear dysregulation of the telomerase/shelterin system was also observed in craniopharyngiomas, highlighting again the TERF2IP as a potential biomarker in this pathology. Finally, the antiproliferative effect of etoposide was dependent on the tumor type analysed. Altogether, our study revealed a profound dysregulation in the shelterin/telomerase complex in IT wherein some of the components might be clinically and functionally relevant, opening new avenues to improve the management of these pathologies.

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Elderly Male with Multiple Endocrine Neoplasia Type 2A: A Diagnostic Journey

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Background
Multiple endocrine neoplasia type 2A (MEN2A) is a rare genetic tumor syndrome due to germline mutations of the RET proto-oncogene, which is characterized by medullary thyroid cancer (MTC), pheochromocytoma (PHEO), and primary hyperparathyroidism (PHPT). The age at onset, aggressiveness of MTC, and the penetrance of other components depend on the genotype. Early prophylactic thyroidectomy and life-long screening for PHEO from childhood are recommended in most cases.
Clinical case
A 73-year-old male was found to have progressively increasing PSA levels during routine check-ups. Prostate biopsy confirmed a prostatic adenocarcinoma (Gleason 3+4 and 4+4). 18F-Choline PET/CT was done next; however, this imaging did not only exclude metastatic disease, but also showed a highly metabolically active thyroid nodule. An ultrasound-guided fine needle biopsy of the nodule confirmed MTC (Bethesda 6). Calcitonin level was high at 1290 ng/l (ref. 8.3 – 14.3 ng/l). Catecholamines and nor/metanephrines were routinely measured in a 24h urine sample before thyroidectomy and were positive. Abdominal CT scan showed a 44 mm partially cystic formation of the left and an 11 mm nodule of the right adrenal gland, both with CT characteristics of PHEO. Laboratory testing for PHPT was negative. After a course of phenoxybenzamine, the patient was planned for laparoscopic total left and partial right adrenalectomy, however, bilateral total operation was finally done due to technical issues. Histopathological report confirmed bilateral PHEO with a PASS score of 8/20 on the left, and 3/20 on the right side. Total thyroidectomy and laparoscopic radical prostatectomy followed in the next weeks. Genetic testing was consistent with MEN 2A (NM_020975.6(RET):c.1900T>G (p.Cys634Gly)). Currently, the patient is doing well on hydrocortisone, fludrocortisone, and levothyroxine supplementation. The family history for MEN2A-related manifestations was negative. Genetic testing results of patient's close relatives are pending.
Discussion
Genetic testing classified our patient as high risk MEN2A-MTC (Level C American Thyroid Association Risk Level) where prophylactic thyroidectomy should be performed before age of 5 and yearly screening for PHEO commenced at eight. The presented patient experienced an indolent, incidentally diagnosed disease, which might be in line with a recent finding that considered age at diagnosis as the most important marker of MTC outcome in MEN2A. Additional yet to be determined factors may enable better understanding of such phenotypic variability.

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Don't let your guard down – aggressive, hereditary paraganglioma associated with SDHD gene nonsense variant: c.33C>A (p.(Cys11Ter))

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Introduction
Paragangliomas belong to the neuroendocrine tumours arising from autonomic nervous system. Various localizations, symptoms that can mimic a wide range of diseases and often unpredictable ability to metastasize are the reasons why paragangliomas pose a significant diagnostic challenge. More than one third of paragangliomas is associated with germline mutations –succinate dehydrogenase (SDH) subunit genes are among the most common susceptibility genes. SDHD was the first among SDH genes identified as being involved in pheochromocytoma/paraganglioma pathogenesis. SDHD mutations are inherited as autosomal dominant trait with a paternal transmission, affected patients usually develop multiple cervical paragangliomas. However, mutations in the SDHD gene do not often predispose to a metastatic evolution.
Case Presentation
We report a case of a 48-year-old woman admitted to the Department of Endocrinology due to suspicion of bilateral cervical paraganglioma – two lesions were visualised on ultrasonography, performed because of concomitant Graves disease. Remarkably, the only sister of the patient died at the age of 47 due to metastatic paraganglioma, 14 years after the diagnosis (SDHD gene mutation was identified), patients' father was diagnosed with bilateral cervical lesions, died suddenly at the age of 39. Laboratory tests revealed slightly elevated free plasma metanephrine concentration 72,1 pg/ml (reference range $<$62 pg/ml), free plasma normetanephrine, plasma 3-metoxytyramine and serum chromogranin A concentrations were within reference range. The result of head and neck CT scan confirmed the presence of two carotid lesions: on the right side measuring 21 x 20 x 32 mm, on the left side measuring 13 x 16 x 18 mm (grade I according to the Shamblin classification). Furthermore, the result of thorax CT scan revealed the suspected lesion below the aortic arch, adjoining the aorta, measuring 10 x 15 mm. All three described lesions showed the pathological tracer uptake in somatostatin receptor scintigraphy (99mTc HYNICTOC 720MBq). The molecular analysis revealed pathogenic SDHD gene nonsense variant: c.33C>A (p.(Cys11Ter)). The patient was referred to the Vascular Surgery Department, where two-stages cervical paraganglioma removal was performed. Other family members also underwent the screening for pheochromocytoma/paraganglioma.
Conclusions
Presented case highlights the importance of molecular testing of patients with pheochromocytoma/paraganglioma and the necessity for long-term follow-up. Furthermore, reported case may hint that the clinical course and risk of

malignancy is not universal for all SDHD pathogenic mutation carriers, and should be stratified in relation to the carried variant, which may improve the accuracy of genetic counselling, clinical screening, and follow-up strategies.

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P388

PRRT 177Lu-DOTA-TATE in pancreatic neuroendocrine tumors – When to initiate?

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Introduction
The best timing for PRRT (*peptide receptor radionuclide therapy*) in the case of pancreatic neuroendocrine tumors (panNETs) is still to define, as randomized prospective trials are lacking. Recent studies suggest that some systemic therapies can affect response to PRRT, favoring an earlier use of the latter.
Objective
To determine the efficacy and toxicity of PRRT, comparing its results when used as a second line systemic therapy (after somatostatin analogs) (Group 1) and as a third or fourth line (after chemotherapy, sunitinib or everolimus) (Group 2).
Methods
A real-world, retrospective study of well-differentiated nonfunctioning panNETS, metastatic and/or unresectable, that completed 3 cycles of PRRT with 177Lu-DOTA-TATE at a tertiary center between 2011 - 2018. The data was collected from clinical records. The statistical analysis was performed in SPSS.
Results
We reviewed a population of 29 patients with a mean age of 55 ± 11 years (52% males). Median time since diagnosis until PRRT was 38 (range: 14-95) months. The majority had grade 2 tumors (64%). Around 89% of patients had hepatic metastasis, 61% lymph node metastasis and 29% other metastases. Median cumulative activity of 19,61 (range: 17-22,2) GBq. A total of 16 patients received PRRT as a 2nd line systemic therapy (Group 1), while 13 patients previously received other systemic therapies (Group 2). Median follow-up time after the first cycle was 31,3 (range: 22-55) months. Median progression-free survival (PFS) was 24,5 (CI 95%: 17 – 32) months and median overall survival (OS) was 46,6 (CI 95%: 20 - 73) months. There was no statistically significant difference of PFS (Group 1: 22,3 (CI 95%: 11-34) Group 2: 24,5 (CI 95%: 15-34); $P = 0{,}95$) and OS (Group 1: 54,8 (CI 95%: 29 - 81); Group 2: 43,3 (CI 95%: 15-72); $P = 0{,}39$) between the 2 groups. Around 90% of patients that reported symptoms before treatment, had symptomatic improvement. One patient had clinically significant hepatic toxicity (G3) after the 1st cycle, partially reversible before the 3rd cycle. There were no cases of clinically significant (grade 3/4) hematological or renal toxicity.
Conclusion
PRRT is a safe treatment, associated with symptomatic improvement. PFS was similar between groups, suggesting that PRRT efficacy is not influenced by previous systemic therapies. However, patients receiving PRRT earlier had the longest OS, although not statistically significant. These data can indicate a potential benefit of using PRRT earlier in the treatment sequence. Randomized prospective studies with larger samples are needed to confirm these results.

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Therapeutic potential of the splicing factor SRSF6 as a novel regulator of the Androgen Receptor in prostate cancer

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Background
Prostate cancer (PCa) is the fifth leading cause of cancer-related death worldwide. The main pharmacological strategy for this pathology is the blockade of the androgen receptor signalling pathway, commonly known as androgen-deprivation therapy. However, some of the patients does no longer respond to this hormonal therapy. Therefore, finding novel therapeutic strategies to tackle PCa, especially its most advanced phenotype [i.e., castration-resistant prostate cancer (CRPC)], is urgently needed. In this sense, although the dysregulation of the splicing process has emerged as a distinctive feature of advanced PCa, the potential role that splicing regulators may play in this disease remain poorly explored. In this study, we aimed to analyse the levels, pathophysiological role, and associated molecular features of the splicing factor SRSF6 in PCa.
Methods
SRSF6 levels (copy-number, mRNA, and protein) were interrogated in seven well-characterized cohorts of PCa patients and in the Hi-MYC transgenic model. The functional/molecular effects of SRSF6 overexpression and silencing were evaluated *in vitro* [using different PCa-derived (LNCaP, 22Rv1, DU145, and PC-3) and non-tumour prostate (RWPE-1) cells] and *in vivo* (tumour growth in xenograft models). RNAseq was performed in 22Rv1 cells to analyse splicing and gene expression alterations in response to SRSF6 silencing.
Results
Our results showed that SRSF6 levels (mRNA/protein) are upregulated in PCa vs. non-tumour prostate samples, linked to clinical parameters of tumour-aggressiveness (e.g., Gleason score, T-stage, perineural infiltration, metastasis at diagnosis), and associated with poor prognosis (i.e., shorter disease-free survival) in PCa patients. Moreover, SRSF6-overexpression increased, while SRSF6-silencing decreased, functional parameters of aggressiveness *in vitro* (proliferation, migration, colonies- and tumorspheres-formation) and tumour growth *in vivo*. Mechanistically, SRSF6 modulation resulted into a dysregulation of Androgen-Receptor (AR) activity through transcriptional control of the AR-coregulators APPBP2 and TOP2B.
Discussion
SRSF6 could represent a new therapeutic target to inhibit persistent AR-signalling in advanced PCa.

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Efficacity of combination of Lenvatinib and PPRT in severe hypersecretion of VIP

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Introduction
VIPomas are rare neuroendocrine tumors (NET), usually located in the pancreas that secrete vasoactive intestinal polypeptide (VIP) leading to high-volume watery diarrhea and complications such as hypokalemia, acidosis and dehydration. The management of VIPoma symptoms is often challenging when surgical resection of all the lesions is not feasible. Treatments are then based on somatostatin analogs (SSA) and may also include hepatic chemoembolization, systemic chemotherapy, targeted therapies, with reported efficacy of sunitinib on hormonal secretion or Peptide Receptor Radionuclide Therapy (PPRT). The combination of these treatments on anti-secretory effects is unknown.
Clinical case
A 61 years-old woman had a non-functioning metastatic grade 2 (Ki67 = 15%) well differentiated pancreatic NET, misdiagnosed during the first 2 years of management as hepatocellular carcinoma (HCC). Therefore, she received Sorafenib and Lenvatinib according to HCC guidelines. After expert pathological review and final diagnosis of NET, she was started on SSA. Six months after SSA initiation, metachronous VIP secretion appeared, contemporary with diffuse liver progression and VIPoma symptoms: severe watery diarrhea leading to continuous hospitalization during four months. Symptoms management required high doses of *I.V.* SSA (octreotide 2400 µg/day). The patient was not eligible for locoregional treatment due to diffuse hepatic miliary invasion. Sunitinib lead to rapidly controlled symptoms but required dose adjustments due to hematological toxicity, and disease progression occurred after 2 months. Chemotherapy with 5FU-Oxaliplatin and the anti VEGF agent Bevacizumab was ineffective. At that time, the 68Ga-DOTATOC PET showed avidity for all lesions. Due to the previously symptomatic response to Sunitinib, Lenvatinib was initiated at reduce dosage (10 mg/day) for hormonal secretion control, together with 2 cycles of 177-Lu-Dotatate (7,4 GBq). This combination resolved rapidly, completely and sustainably VIPoma symptoms, associated with a massive decreased of plasma VIP level after one month (from 20 to 3 times over the upper limit normal) and a morphologic partial response after three months. Lenvatinib led to constipation and, whenever, the patient stopped taking the drug, the diarrhea recurred.

Therefore, maintenance Lenvatinib alone is ongoing with no functional symptoms since four months.
Conclusion
Urgent management of severe uncontrolled VIP secretion can lead to unusual treatment combinations in order to control both hormonal secretion and tumor growth. The anti VEGF activity may not be the only mechanism of VIP secretion inhibition of Sunitinib owing to the lack of efficacy of Bevacizumab in our case. The long-term toxicity of the combination reported here is unknown and remains to be studied.

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P391

Urinary free cortisol is an independent predictive factor for early distinction between ectopic ACTH secretion and pituitary Cushing's disease

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Introduction
The poor prognosis of patients with Cushing's syndrome due to ectopic ACTH secretion (ECS) requires prompt diagnosis and management of the disease.
Objectives
To find clinical and biological differences between ECS and pituitary Cushing's disease (CD) at diagnosis and to determine whether any of them may be a potential predictor for early suspicion of ECS.
Methods
This was a retrospective case-nested study of 18 patients with ECS diagnosed and treated between 1993 and 2017, compared with 36 patients with proven CD and matched for the time of diagnosis.
Results
ECS occurred more frequently in men (13/5 vs. 10/26) and at an older age (53.4 $\pm$ 17.3 vs. 43.1 $\pm$ 13.9) than CD. In most patients (89%) the source of ectopic ACTH secretion was identified by thoraco-abdominal CT. No significant difference was found in the prevalence of symptoms and signs of hypercortisolism between the two groups. We found that potassium level $\leq$ 3.65 mmol/l had sensitivity and specificity of 77%, and LDH level greater than 1.28xULN had a sensitivity of 69% and a specificity of 68% for the diagnosis of ECS. Both parameters were correlated with 24-hour urinary-free cortisol (UFC) which was higher in the ECS group (median: 1127 µg/24h) compared to the CD group (216 µg/24h, $P<0.05$). On univariate analysis, an older age at diagnosis, male sex, lower serum potassium, higher LDH and higher UFC values were significant predictors of ECS. Male sex increased the relative risk of ECS by 6.8 times and hypokalemia increased this risk by 52 times for each 1.0 mmol/l-decrease in serum potassium. However, only UFC (expressed as $\log_{10}$) was kept as an independent predictive factor in the multivariate analysis ($P=0.0009$), and a discriminant decision-tree approach showed that a UFC level $\geq$ 633 µg/24h (10.5-fold the upper limit of normal) was the best cut-off with a sensitivity of 87% and a specificity of 92% for the diagnosis of ECS. There was no difference between the two groups in terms of complications related to hypercortisolism but patients with ECS had a lower remission rate and a higher mortality.
Conclusions
While severe hypokalaemia and higher LDH values translate a more severe degree of hypercortisolism in patients with ECS, 24h UFC at diagnosis appears to be the main independent predictor of ECS, with the best cut-off value determined at 10.5-fold the ULN, above which clinicians should rapidly suspect ECS and perform the appropriate work-up including thoraco-abdominal CT.

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Influence of CaSR in testicular germ cell tumors

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More than 90% of malignant testicular tumors arise in the germ cells and are denoted testicular germ cell tumors (TGCTs). TGCTs are one of the most common cancers among men between 15 to 40 years of age and arise from a common precursor cell, the germ cell neoplasia in situ (GCNIS), an arrested and transformed fetal gonocyte that become invasive after puberty. TGCTs are divided into seminomas and nonseminomas based on histology. Fortunately, TGTCs are highly sensitive to cisplatin-based chemotherapy and therefore the survival rate is high. However, adverse effects involve an increased risk of infertility and other comorbidities, highlighting the importance of chemotherapy-reducing strategies. The calcium sensing receptor (CaSR) is a key player in the regulation of calcium homeostasis, exerting its primary function in the parathyroid gland and the kidneys. CaSR has been implicated in the pathogenesis of various cancers including colorectal- and breast cancer, exerting both oncogenic- and tumor suppressor functions. However, the role of CaSR in TGCTs have not previously been described. CaSR can be targeted using the negative allosteric modulator, NPS-2143, and the FDA-approved positive modulator, Cinacalcet. Therefore, we investigated the influence of CaSR in TGCTs as a potential target for chemotherapy-reducing treatment. The expression of CaSR was investigated by qPCR, western blot, and immunohistochemistry (IHC) in TGCT cell lines and human samples of normal testis, GCNIS, and TGCTs. The effect of treatment of TGCT-derived cell lines with Cinacalcet, NPS-2143, or calcium was assessed in vitro using proliferation assays. Finally, the effect of positive allosteric modulation of CaSR using Cinacalcet was determined *in vivo* using TGCT xenograft mouse models. CaSR was expressed in normal testis, GCNIS, TGCTs, and TGCT cell lines. mRNA levels of CaSR were correlated with markers of pluripotency, NANOQ and Oct-4. Additionally, expression levels of CaSR were strongly correlated with PTHrP in GCNIS and embryonal carcinoma tissue suggesting a link between these two factors. Western blot and IHC demonstrated expression of CaSR in normal testis, GCNIS, and TGCTs. In vitro experiments revealed a slight increase in proliferation of embryonal carcinoma-derived NTera2 cells treated with cinacalcet and a corresponding decreased proliferation when treated with NPS-2143. Accordingly, treatment with Cinacalcet increased tumor volume in an NTera2 xenograft mouse model. This study indicates potential growth regulating effects of CaSR in TGCTs and suggests that cellular calcium homeostasis in TGCTs may be a promising target for developing novel chemotherapy-reducing strategies.

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Hypogonadism as a first manifestation of Poems Syndrome

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Introduction
Poems Syndrome is a rare multisystem disorder characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma-proliferative disorder and skin changes, among other features. Literature describes endocrine abnormalities at least in 93% of patients with Poems Syndrome during the diagnosis as well as during the follow-up. The most common deficiencies ranked by their frequency are hypogonadism, hyperprolactinemia, hypothyroidism, abnormal glucose metabolism and in rare cases adrenal insufficiency and elevated IGF-1 levels.
Case Presentation
67-year-old man with history of right occipital stroke and 1-2 pack a day smoker with pulmonary disease with severe obstruction in spirometry is referred to endocrinology consultations because of erectile dysfunction with decreased libido and asthenia. At physical examination he presented with a group of cervical adenopathies and paresthesia in palms and soles that prevent walking of about one year of evolution. No mucosal hyperpigmentation but presence of hyperpigmented lesions in thorax and abdomen. Normal testicular size and presence of secondary sexual characteristics. No other relevant associated symptoms. Laboratory parameters confirmed by two determinations revealed: Hb 18.1 g/dl (12,0-18,0), Hematocrit 59% (37,0-52,0), HbA1c 5,73% (4,0-6,5); TSH 0,459 mU/l (0,380-5,330); T4L 1,22 ng/dl (0,54-1,24); Prolactine 14,7 ng/ml (2,6-13,1);

GH 0,386 ng/ml (1,0-3,0); IGF-1 94,9 ng/ml (67,0-141,0). FSH 2,31 UI/l (1,27-19,26); LH 2,48 UI/l (1,2-8,6); Testosterone 1,42 ng/ml (1,75-7,81); establishing the diagnosis of secondary hypogonadism. Corticoid axis was not valuable due to chronic corticoid treatment for respiratory disease. Pituitary MRI was performed with no findings. The electromyogram showed polyneuropathy in palms and soles with axonal and demyelinating involvement. Hematology completed examination with lymph node biopsy resulting in plasmocellular variant of Castleman disease with low HHV-8 expression and monoclonal spike IGG Lambda (6,8% 0,4 g/dl). Diagnosis of Poems Syndrome was done following the diagnostic criteria:

- Mandatory criteria: monoclonal spike and sensory-motor polyneuropathy.
- Mayor criteria: Castleman disease.
- Minor criteria: secondary hypogonadism, cutaneous hyperpigmented lesions and polyglobulia.

The patient was discharged after clinical stability and improvement of symptoms. He continues with chemotherapy treatment in Hematology outpatient clinics and follow-up by Neurology and Endocrinology. Testosterone treatment was not started due to severe polyglobulia secondary to hematological disease.

Conclusions

Poems Syndrome involves multiple organs, and a multidisciplinary approach should include an endocrinologist. Patients should be systematically assessed for endocrinopathy and treated as indicated. Long-term follow-up is recommended since the appearance of new endocrinopathies as well as the remission of others.

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Investigating the risk of metabolic and cardiovascular comorbidities among patients with parathyroid cancer: a nationwide representative cohort study in Taiwan

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Background

This study aimed to determine whether primary parathyroid cancer patients were associated with increased metabolic and cardiovascular comorbidities in comparison to the general population

Method

We used the National Taiwan Cancer Registry Database to construct a cohort of patients with parathyroid cancer from January 1, 2004, to December 31, 2019. We compared the incidence of hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, coronary heart disease, and heart failure with the general population matched based on a propensity score in a one-to-five fashion.

Results

A total of 72 parathyroid cancer patients and 360 matched general population (mean age: 55 years; 59% women) were included, with different exclusive numbers for each metabolic and cardiovascular comorbidity cohort. The number of cases based on a total of 2347.7 person-years of observation, included 53 deaths, 29 hypertension, 9 diabetes, 13 hyperlipidemia, 10 atrial fibrillation, 18 coronary artery disease, and 13 heart failure. According to multivariate analysis, parathyroid cancer remained significantly associated with diabetes [Hazard ratio (HR): 9.28; 95% confidence interval (CI): 1.72-50.07], hyperlipidemia (HR: 5.86; 95% CI: 1.61-21.31), and heart failure (HR: 4.46; 95% CI: 1.18-16.84). Sub-distribution of competing mortality events and subgroup analysis showed robust evidence of metabolic and cardiovascular comorbidities. Model were estimated by years since cancer diagnosis and the highest odds appeared within six years and dramatically dropped after the sixth year. However, the long-term trend for an association between parathyroid cancer and comorbidities persisted for decades. The national cohort study demonstrated that adult parathyroid cancer patients had a significantly higher incidence of diabetes mellitus, hyperlipidemia, and heart failure than the general population.

Conclusion

An increased risk of metabolic and cardiac comorbidities among parathyroid cancer patients required great caution.

Key words

Parathyroid cancer' cardiovascular disease' diabetes mellitus

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Abstract withdrawn

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Selective Arterial Calcium Stimulation Test In Two Cases With Occult Insulinoma

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Introduction

Insulinoma is a rare neuroendocrine tumor that is difficult to diagnose due to its obscure location. Conventional radiographic methods have low sensitivity and are inadequate to detect insulinoma. Selective arterial calcium stimulation test (SACST) is 95–100% sensitive in the diagnosis of insulinomas. Here, we presented two cases of insulinoma that could not be located by radiographic methods and evaluated them with SACST.

Case 1

A 48-year- old woman who had dizziness was referred to our endocrine clinic with a suspicion of insulinoma. A 72-hour fasting test was performed to establish a diagnosis of endogenous hyperinsulinemia. After 19 h hypoglycemic symptoms emerged and fasting serum glucose (FSG) was 27 mg/dl, insulin 6,5 mU/l, and C-peptide 2 µg/l. MRI of the abdomen, Galium-68 Dotatate scintigraphy, and endoscopic ultrasonography (EUS) failed to detect the tumor. SACST was performed to localize the tumor. Calcium injection of the gastroduodenal artery caused a more than 11-fold increase in hepatic insulin above baseline indicating a lesion in the head region of the pancreas. Intraoperative ultrasonography of the pancreas revealed a 1 cm nodular lesion in the head. Proximal pancreatectomy was performed. Histopathological findings were consistent with well-differentiated neuroendocrine tumor showing positive staining with synaptophysin and chromogranin. After surgery, the patient was free of all previous symptoms.

Case 2

A 67-year- old woman was admitted to the clinic due to dizziness and diaphoresis. She applied to the emergency department once with a loss of consciousness. There was a weight gain of 4-5 kg during this period. After 12 h of the 72-hour fasting test, hypoglycemic symptoms emerged, and FSG was 36 mg/dl, insulin 6,9 mU/l, and C-peptide 1,7 µg/l. MRI of the abdomen, Galium-68 Dotatate scintigraphy, and EUS failed to demonstrate the tumor. SACST was performed and calcium injection of the splenic artery caused a more than 9-fold increase in hepatic insulin above baseline which was suggestive of an insulinoma lesion in the tail of the pancreas. Intraoperative ultrasonography of the pancreas revealed a 1 cm nodular lesion in the tail. Distal pancreatectomy was performed. No hypoglycemia has occurred since the surgery.

Conclusions

The localization of insulinoma is critical for curative surgery and might be problematic. Because of the low sensitivity of non-invasive imaging procedures in tumors smaller than 2 cm, invasive methods can be used for the localization like in our cases.

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Therapeutic Efficacy of the Combination of Braf and Mek Inhibitors in Erdheim-Chester Disease (EEC)

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EEC is a multisystemic disease secondary to a clonal histiocyte proliferation of non-Langerhans cells due to hyperactivation of the MAPK/ERK signaling pathway, with somatic BRAF V600E mutation present in 50% of cases with therapeutic implications. Between 50% of patients develop endocrinopathies, the most frequent being central diabetes insipidus (CDI). We present the case of a 42-

year-old woman, diagnosed with CDI in 1998 without family history, treated with DDAVP [MRI: absence of neurohypophysis, normal pituitary stalk), negative AVP gene and hypergonadotropic hypogonadism since the age of 39 years. In 2019 she developed acute renal failure (GFR 20 ml/min/1.73 m^2) and HTA, bilateral grade IV hydronephrosis due to bilateral perirenal infiltrative process. She required a double J catheter and subsequent bilateral nephrostomy without improvement of renal function. She had associated blastic bone lesions in axial and appendicular skeleton. During the diagnostic process she developed gait ataxia, dysarthria and dysphagia. In view of the suspicion of multisystemic disease of histiocytic origin, a bone biopsy of the sacral lesion (not profitable) was conducted and biopsy of the perirenal infiltrative tissue showed proliferation of histiocytes (CD68 positive, S100 and CD1 negative, no Langerhans phenotype) compatible with EEC and presence of BRAF V600E mutation in molecular analysis. The PET-CT extension study (18FDG) showed cerebral hyperenhancement predominantly in the posterior fossa, generalized bone involvement and pathological uptake in bilateral perirenal fat, retroperitoneal, left adrenal, gonads, pulmonary artery, interatrial septum and pericardial thickening. Bone marrow biopsy showed grade 3 myelofibrosis without myeloproliferative syndrome criteria. The presence of BRAFV600E mutation allowed treatment with Vemurafenib without side effects despite renal failure, with clinical improvement and reduction of lesions in PET-CT at 8 weeks of treatment. At the 5th month, after worsening of the neurological symptoms (pyramidocerebellar syndrome), she was treated with IV dexamethasone and second line with Drabrafenib-Trametinib was started (2020). Clinical neurological improvement was confirmed a few weeks after initiation, her nystagmus, dysarthria, dysmetria, and gait improved remarkably, and progressive reduction of pathological uptakes at brain and renal level during follow-up with FDG-F18. In 2021 she was diagnosed with central hypothyroidism and somatotropic deficit, renal function has remained stable and nephrostomies have been closed (2022). The patient continues with the combination of BRAF and MEK inhibitors. She has also developed several endocrinopathies over time: CID as first manifestation 21 years earlier, adenohypophyseal deficits, gonadal involvement with amenorrhea and unilateral adrenal involvement. Prognosis depends on the neurological and cardiological evolution.

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Severe insulin secretion by an inoperable metastatic insulinoma can be controlled by 177-Lu-DOTA-TATE radionuclide therapy: a case report

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Introduction

Metastatic insulinoma is an extremely rare form of malignant insulinoma involving metastatic growth where classical surgical treatment is often impossible. Medical therapies are widely considered and reserved for those especially with inoperable insulinoma with the goals of reducing tumor size, but also of reducing hypoglycemic events either by acting directly on the insulinoma cells (reducing excess insulin secretion from the insulinoma cells or reducing tumor volume), by decreasing sensitivity to insulin or by directly increasing blood sugar levels (glucose perfusion, enteral nutrition). Ga-DOTATOC radionuclide imaging is widely used for insulinoma diagnosis, however, the equivalent therapeutic radionuclide Lu-DOTATATE is less commonly used.

Observation

We report the case of a 58 yo patient with no previous medical history hospitalized in our department for treatment of a malignant symptomatic secreting insulinoma with bone, liver and lymphatic metastasis. The patient presented a severe excess of insulin secretion leading to a rapid escalation in conventional therapy (DIAZOXIDE, calcium channel blockers, corticotherapy, mTOR inhibitors, second-generation somatostatin analogs, continuous enteral nutrition and continuous glucose perfusion) that struggled to maintain blood sugar levels above 50 mg/dl. Tests for germline mutations and somatic mutations were negative and four months of intensive conventional treatment lead to no clinical or morphological success. However, after observing good 68-Ga-DOTATOC uptake, peptide receptor radionuclide therapy was proposed using 177-Lu-DOTA-TATE. The first single dose of 7400 MBq was extremely effective on insulin secretion allowing the discontinuation of DIAZOXIDE, mTOR inhibitors and G30% glucose perfusion as well as significant reduction in enteral nutrition and corticotherapy. The clinical tolerance of the treatment was excellent and did not cause initial excess insulin release.

Discussion

Radionuclide therapy by 177-Lu-DOTA-TATE was an effective and well tolerated treatment in this patient presenting secreting inoperable malignant insulinoma and could be considered in other patients in similar situations presenting hypoglycemia despite conventional treatment.

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P651

Impact of vascular invasion on otherwise low-risk papillary thyroid carcinomas: a retrospective and observational study

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Background

Presence of venous vascular invasion is a criterion of intermediate risk of recurrence in papillary thyroid carcinoma (PTC). However, the presence and type of vascular invasion (lymphatic or venous) is often underreported and its impact on PTCs without other risk features remains unknown.

Objective

To evaluate the impact of both lymphatic and venous invasion on the risk of recurrence/persistence on otherwise low-risk PTCs.

Methods

Retrospective study including patients with otherwise low-risk PTCs but with vascular invasion, diagnosed between 2013 and 2019. The persistence/recurrence during the follow-up was evaluated. Pathology was reviewed to confirm the presence of vascular invasion and determine the type of invasion.

Results

A total of 141 patients were included. Vascular invasion was confirmed in 20.6%. After surgery, 48.9% ($n=69$) of the patients received radioactive iodine (RAI). The median follow-up time was 4 [3-6] years. Overall, 6 (4.2%) patients experienced persistent/recurrent disease in the neck, including 3 with vascular invasion, confirmed as "only lymphatic". Overall, patients with tumors harboring vascular invasion had significantly more persistent/recurrence disease compared with those without vascular invasion (10.3% vs 2.7%, $P=0.1$), especially in the subgroup of patients not treated with RAI (20% vs 1.6%, $P=0.049$) [OR 15.25, 95% CI 1.24-187.85, $P=0.033$].

Conclusions

Vascular invasion, including lymphatic invasion only, is associated with a sensibly higher risk of persistent/recurrent disease in otherwise low-risk PTCs, namely in patients not treated with RAI. Lymphatic invasion could have a role in risk-stratification systems for decision making.

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P652

Characterization of splicing machinery components in thyroid cancer and their correlation/association with tumour behaviour and clinical features

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Emerging evidence indicates that the cellular machinery controlling the splicing process (spliceosome) is altered in several tumour types, leading to oncogenic

splicing events associated with tumour progression and aggressiveness. However, whether this molecular phenomenon also occurs in thyroid cancer has not been yet explored. Therefore, our main aim was to explore the potential dysregulation of the expression of relevant spliceosome components and splicing factors in clinically well-characterized human thyroid cancer samples (papillar, follicular and medullary), compared to its adjacent non-tumour tissue, and whether these alterations might be associated with relevant clinical parameters. Results revealed a clear dysregulation of several components of the splicing-machinery in thyroid cancer samples compared to its adjacent non-tumoral tissue, wherein the expression of specific components was associated with key clinical parameters. Based on these results, we next explored different functional (e.g. proliferation, migration, and tumour-spheres and colonies formation) and mechanistic (gene expression/signalling pathways) assays in human thyroid cancer cell models (TCP1 and Cal62) in response to the inhibition of the splicing machinery activity [i.e. using the splicing-factor-3B-subunit-1 (SF3B1; a core component of this machinery) inhibitor pladienolide B] and SF3B1 silencing (using an specific siRNA). These *in vitro* studies revealed that pladienolide-B significantly decreased cell aggressiveness parameters (proliferation, migration, formation of tumour-spheres and colonies) in thyroid cancer cells through the modulation of the expression levels of different component of key oncogenic signalling routes. Similarly, SF3B1 silencing also reduced the above-mentioned tumour-related features, thus confirming the critical role of SF3B1 and consequently, of the splicing machinery, in thyroid pathophysiology. Altogether, our data demonstrate a drastic dysregulation of the splicing-machinery in thyroid cancer tissues that might be associated to its tumorigenesis, paving the way to explore the use of specific splicing-machinery components as novel diagnostic/prognostic and therapeutic targets in this pathology. In particular, the genetic and/or pharmacological inhibition of SF3B1 may represent a promising novel therapeutic strategy worth to be explored through randomized controlled trials that could improves the outcome of patients affected by clinically aggressive thyroid cancer.

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P653

Innate differences in the molecular signature of inferior and superior human parathyroid glands: potential implications for parathyroid adenoma

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Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterised by hypercalcemia, skeletal fragility, and renal stones with majority (75%) of parathyroid tumours localized to the inferior parathyroid glands. The reasons for this natural bias are not known till date. A probable reason may be due to inherent differences in the molecular milieu of normal superior and inferior parathyroid glands. Such questions cannot be answered using superior and inferior parathyroid adenoma tissues from different patients due to the confounding effect of inter-individual differences. Comparison of inferior parathyroid adenoma tissue with normal superior gland from the same patient would also be inappropriate, as any differences observed could be secondary to tumorigenesis. Thus, the ideal approach would be comparison of normal superior and inferior parathyroid glands from the same individual. However, it is difficult to obtain normal parathyroid tissue. To overcome this limitation, we assessed the global gene expression profile of superior and inferior glands obtained from forensic autopsies. Genes with significant differential expression between superior and inferior parathyroids were further confirmed by RT-PCR in 19 pair of glands. As an iterative approach, additional genes with an established role in parathyroid disorders, i.e., *CASR*, *MAFB*, *PAX9*, *TBCE*, *TBX1*, *VDR*, *MEN1*, *CCND1*, and *CDC73* were also evaluated by RT-PCR in all 19 pairs of superior and inferior parathyroid glands. Seven homeobox genes, namely *HOXA4*, *HOXA5*, *HOX-BAS3*, *HOXB4*, *HOXB6*, *HOXB9*, *IRX1*, and one encoding for *ALDH1A2* showed a lower expression in the inferior parathyroid glands than the superior. Conversely, *SLC6A1* showed a higher expression in the inferior glands. Of the nine genes with significant differential mRNA expression among superior and inferior glands HOXB9, HOXB4 and IRX1 could be detected by western blotting/mass spectrometry. The study is the first to provide novel clues for the differential expression of seven Homeobox genes *HOXA4*, *HOXA5*, *HOX-BAS3*, *HOXB4*, *HOXB6*, *HOXB9*, *IRX1 along with ALDH1A2*, and *SLC6A1* in inferior vs the superior parathyroid glands. The Homeobox genes are evolutionarily conserved family of transcriptional-factors essential for embryogenesis and tumorigenesis. The above results suggest that the first hit in parathyroid oncogenesis might be developmental. The mutations in *MEN1*, *CDC73*, or *CCND1* in the inferior gland may be a second hit. This study suggests potential clues for the preferential localization of parathyroid tumours to the inferior glands as in primary hyperparathyroidism. Future studies on identification of methylations of homebox genes may also help elucidate the underlying mechanisms of primary hyperparathyroidism.

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P654

Intermediate-risk Differentiated Thyroid Cancer with Stimulated Thyroglobulin or N1b Needs High Adjuvant Radioactive Iodine Dose

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Background
There are no definite recommendations on the optimal dosage of initiating adjuvant radioactive iodine (RAI) therapy for intermediate-risk differentiated thyroid cancer (DTC) patients in current relevant guideline. This study aimed to investigate the response of intermediate-risk DTC patients with a low (3.7GBq) or high RAI dose (5.55GBq).
Methods
Propensity score matching was performed to control for baseline characteristics. A total of 476 patients with intermediate-risk DTC were retrospectively reviewed. 238 patients received RAI of 3.7GBq (Group 1), and the other 238 patients received RAI of 5.55GBq (Group 2). Then patients were further divided into 4 subgroups: Subgroup 1: stimulated thyroglobulin (sTg) <10ng/ml, Subgroup 2: sTg ≥ 10ng/ml, Subgroup 3: N0 + N1a, Subgroup 4: N1b. We compared the response to different RAI dose in subgroups. The univariate and multivariate logistic regression were conducted to screen out factors associated with excellent response (ER). Finally, the prognostic nomogram was used to explain ER rates as a useful tool in clinical practice.
Results
Before dividing the subgroups, The ER rate in Group 1 was higher than Group 2 (65.1% vs 47.1%, $P<0.05$). There was no significant difference of response to different RAI dose in subgroup 1. Group 1 has significantly higher incomplete response (IR) rates in Subgroup 2 and 4(71% vs 41.5%, 24.1% vs 10.9%, all $P<0.05$ respectively). However, in Subgroup 3, the ER rate in Group 1 and the IR rate in Group 2 were relatively higher. (69.2% vs 53.2%, 7.5% vs 15.6%, all $P<0.05$ respectively). By univariate and multivariate logistic regression analysis, N1b (OR:0.158, 95%CI: 0.034-0.736, $P=0.019$), sTg> 10ng/ml (OR:0.048, 95%CI: 0.022-0.104, $P<0.001$), and T2 (OR: 0.472, 95%CI: 0.228-0.981, $P=0.044$) were manifested to be independent risk factors for ER. The nomogram showed that sTg, N status and T status were the top 3 contributors to the ER.
Conclusions
Higher RAI dose should be considered for intermediate-risk DTC patients when sTg ≥ 10ng/ml or with N1b status.

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P655

Primary hyperparathyroidism. Parathyroid carcinoma (clinical case)

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Introduction
A rare cause of hyperparathyroidism in pediatric is parathyroid carcinoma. The variety of clinical manifestations of hyperparathyroidism and the associated hypercalcemia slows down the verification of its primary nature.
Material and methods
Medical records of an inpatient 13y.o child.
Results
Child from 5 pregnancies, 1 delivery. Pregnancy was accompanied by endemic goiter. Delivery at 39-40weeks, physiological. Previous pregnancies-miscarriages. The child was ill during the last year of life. In the debut of the disease, arthralgia of the knee joints, gait disturbance. In the dynamics for 9 months, there is an increase in

the deformity of the knee joints, he received inpatient treatment with a diagnosis of "Bilateral dysplastic coxarthrosis with juvenile epiphysiolysis of the femoral heads. Pathological fracture of the upper and middle third of the diaphysis of the left femur with angular displacement between the fragments against the background of fibrous dysplasia". 10th month of illness, the condition worsened, complained of abdominal pain, thirst, vomiting, weakness, pallor. Urgently hospitalized with a hypercalcemic crisis. In the clinic of the disease there were bone, renal, cardiovascular, gastrointestinal forms, laboratory hyperparathyroidism (up to21448ng/dl), metabolic disorders (hypokalemia, hyponatremia, hypercalcemia up to3.76mmol/l, hyperglycemia, hypoproteinemia, high alkaline phosphatase up to1597.4u/l, alpha-amylase up to318.7u/l, hypercreatininemia, anemia. Instrumental studies confirmed the volumetric formation of the parathyroid gland. Ultrasound of the thyroid gland-hyperplasia and diffuse changes in the parenchyma of the thyroid gland. Node (adenoma?) of the right lobe of the thyroid gland. Adenoma of the parathyroid gland on the right; MRI of the neck and mediastinum-a picture of the neoplasm soft tissues of the neck on the right (adenoma of the parathyroid gland (size3.1-2.0-2.0cm). The child underwent surgery to remove the adenoma of the parathyroid gland, hemithyroidectomy on the right. Cytology (material of the parathyroid gland): corresponds to parathyroid adenoma. Histology (microscopy): parathyroid tumor, nodular structure, with a well-defined fibrous capsule and fibrinous septa dividing the tumor into lobes and trabeculae. Tumor cells with signs of moderate polymorphism. There is a focus of invasion of tumor cells into the capsule. IHC study: Cyclin D1, P53-positive, Ki-67-5%. Conclusion: morphological picture and immunophenotype of parathyroid carcinoma. There are no tumor elements in the thyroid tissue, ICD-0 Code8140/3(Ki-67-5%).

Conclusion

Parathyroid adenoma can be clinically asymptomatic, as well as under the masks of other diseases. In the case of extremely high levels of calcium in the blood and the presence of pronounced symptoms by pediatricians should be alert to hyperparathyroidism.

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P656

Management of NENs with SSTR2-antagonist: how close are we to a clinical solution? The first results of the TECANT study: Novel 99m-Tc-labelled somatostatin antagonists in the diagnostic algorithm of neuroendocrine neoplasms – a feasibility study

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Introduction

The management of patients with neuroendocrine neoplasms (NEN) has been revolutionised since the introduction of radiolabelled somatostatin analogues targeting overexpressed somatostatin receptors (SSTR). Accurate assessment of SSTR status of primary focus/metastases is crucial to determine the choice of the treatment method. Recently it has been shown that novel molecular probes, SST_2-antagonists, recognize more binding sites in comparison to the widely used $SSTR_2$-agonists and hence improve diagnostic efficacy, especially when the density of SSTR is low. The aim of the project is to develop a novel 99mTc-labelled $SSTR_2$-antagonist as a sensitive probe to assess the SSTR status in NEN patients.

Material and Methods

In frame of the first, extensive preclinical studies the most promising SSTR antagonist N4-LM-3 (p-Cl-Phe-cyclo(D-Cys-Tyr-DAph(Cbm)-Lys-Thr-Cys)-D-Tyr-NH_2 (TECANT-1) was selected for clinical translation to initiate a clinical feasibility study including the development of a robust, reproducible quantitative imaging method of SSTR assessment in NEN tissues[1]. The clinical study is a phase I multicentre trial. Ten patients with advanced NEN and SSTR positivity confirmed by routinely used SSTR imaging based on a radiolabelled agonist will be enrolled in the study. Safety, tolerability, human pharmacology, dosimetry and NEN targeting properties of the compound tested will be assessed. Comparability of clinical and imaging data collected at imaging centres will be ensured through an established, centralized secured database also providing standardized image analysis protocols and integrated statistical tools.

Results

Within the TECANT project, the preselected ^{99m}Tc-labelled $SSTR_2$-antagonist TECANT-1 was successfully developed into a kit formulation amenable for use in a hospital radiopharmacy setting. Together with the favourable toxicological and promising pharmacological profile, [^{99m}Tc]Tc-TECANT-1 is ready to be advanced into first-in-human multicentre clinical trial (EudraCT no: 2019-003379-20). After receiving positive opinion from the national authorities, the clinical part of the study has been initiated. No clinical side effects were observed after the first [^{99m}Tc]Tc-TECANT-1 application; a very good visualization of NEN metastases was obtained.

Conclusions

The first obtained images with radiolabelled $SSTR_2$-antagonist appear to be of great clinical significance. The 99mTc-labelled $SSTR_2$-antagonist is expected to enable a reliable and widely available method for quantitative assessment of SSTR status and to improve the decision-making diagnostic and therapeutic algorithm as one of the key elements in a personalised approach to the management of NEN patients.

Reference

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[1]Melpomeni *et al*: Selection of the First ^{99m}Tc-Labelled Somatostatin Receptor Subtype 2 Antagonist for Clinical Translation-Preclinical Assessment of Two Optimized Candidates. Pharmaceuticals 2020;14(1):19;doi:10.3390/ph14010019

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Novel insights to study the potential of the somatostatin system in NETs and NECs

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Neuroendocrine tumors (NETs) and carcinomas (NECs) are a heterogeneous group of malignances whose incidence is increasing worldwide. First-line approach is represented by surgery, whereas an effective pharmacological treatment for disseminated and relapsing disease is still needed. Somatostatin (SS) receptors (SSTs) constitute the main suitable pharmacological targets for NETs therapy with SS analogs (SSAs). Nevertheless, a large proportion of NETs and most NECs, are unresponsive or resistant to SSAs and the causes that underline resistance still remain poorly understood, highlighting the need of alternative strategies. Recently, the neuropeptide cortistatin (CST), that shares with SS actions and affinity to SSTs, emerged as an anti-inflammatory player, showing potential antitumoral behavior. The aim of this study was to characterize the SS and CST system in different NETs and NECs cell models. More precisely, the effects of SS/CST and selected analogs were tested on cell proliferation and apoptosis on classical (BON-1, QGP-1) and novel Pan-NETs (NT-18P, NT-18LM) and Pan-NEC (NT-38) cell lines. Our data shows that SSAs exerted limited actions on cell proliferation in novel cell lines. On the other hand, CST treatment induced dose and time-dependent effects: while it caused limited actions in BON-1 and QGP-1 cells, it exerted significative inhibition of cell proliferation, and induced apoptosis in NT-18P, NT-18LM, and NT-38 cells. Interestingly, each model used displayed a unique SSTs expression profile, which may underlie their different response to treatments. Our study provides an initial characterization of novel Pan-NETs and Pan-NECs cell models, more accurately resembling human tumors behavior, in response to various drugs, paving the way for novel original avenues to explore new therapeutical approaches for NETs/NECs treatment.

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Cellular models of parathyroid carcinoma: preliminary results

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Parathyroid carcinoma (PC) is an extremely rare endocrine malignancy of the parathyroid glands, representing less than 1% of all parathyroid neoplasms. PC is characterized by an excessive secretion of parathyroid hormone (PTH) and severe hypercalcemia. In contrast to parathyroid adenoma, the prognosis for patients with PC is poor, with an overall survival rate of 78-85% and 49-70% respectively at 5 and 10 years after diagnosis, due to the commonly unmanageable hypercalcaemia, which is the cause of death in most cases. There are currently no decisive therapies available for PC. The main treatment for PC remains surgical removal of the tumour gland(s), but persistent, or recurrent post-surgical disease is reported in about 50% of patients. A better understanding of the biology and pathophysiology of PC is necessary to advance is not only too better in distinguishing PC from benign counterpart, but also to develop novel targeted and effective therapies. The principal aim of this research is to establish an *in vitro* model of human primary cell line of PC, to evaluate the presence of cancer stem cells (CSCs), and to isolate and characterize them. We established a primary cell culture of from a primary sporadic PC lesion. Hence, the PC phenotype was evaluated by immunofluorescence staining for PTH, ki67, Desmin, CaSR protein, parafibromin, and by evaluation of PTH release. We evaluated the ability of PC cells to form spherical colonies under non adherent conditions to identify and isolate PC cancer stem cells (PC-CSCs). Cells isolated through this particular assay were then characterized by: 1) immunofluorescence staining for mesenchymal stem cell (MSC) markers, 2) immunofluorescence staining for PTH, ki67, Desmin, CaSR protein, parafibromin, 3) quantitative RT-PCR analyses of gene expression of the embryonic stem cell (ESC) marker genes (i.e., *KLF4*, *POU5F1*, Nanog and *SOX2*) and of the *PTH* gene, and 4) ELISA dosage of the PTH extracellular release. The obtained preliminary results showed that we established a primary human PC cell line and that we isolated, for the first time, a PC-CSCs line, presenting the phenotypic characteristics typical of CSCs and the classical features of parathyroid principal cells, such as CaSR expression and PTH expression and release. Further investigations are ongoing to completely characterized both the primary PC cell line and the PC-CSCs. In conclusion, these established cell models could pave the way to better understand the biology of PC cells, and the basis of parathyroid malignant carcinogenesis and aggressiveness of PCs.

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Two cases of paraneoplastic hypoglycemia

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Introduction
Nonislet cell tumour hypoglycemia (NICTH) is a rare complication of malignancy. The most common cause is overproduction of IGF2, which activates insulin receptors, resulting in hypoinsulinemic hypoglycemia. When a solitary fibrous tumor is responsible, it is called Doege-Potter syndrome.
Case 1
58-year-old woman, with a history of gastrointestinal stromal tumor and pleural solitary fibrous tumor with pulmonary and lymph node metastases. She presented in the ER with altered mental state and hypoglycemia (minimum glucose value of 32mg/dl). Bloodwork showed: glucose 34 (76-115) mg/dl, C peptide 0.294 (1.1-5.0) ng/ml and insulin <0.400 (2.6-24) uUI/ml. The patient was started on therapy with corticosteroids and was later discharged with prednisolone 60mg daily. Further bloodwork showing IGF2 639 (230-970) ng/ml and IGF1 20.3 (63.3-190) ng/ml, with an IGF2/IGF1 ratio of 31.5 (>10) confirmed the diagnosis of Doege-Potter syndrome. The patient improved significantly after treatment with chemotherapy, with progressive tapering of prednisolone.
Case 2
55-year-old man, with a history of diabetes mellitus type 2. He was admitted after he presented in the ER with acute confusional state in the context of hypoglycemia (minimum glucose value of 25mg/dl). Physical examination showed an abdominal mass. An abdominal MR confirmed the presence of an abdominopelvic mass, with 27x13cm, and a biopsy was performed, suggestive of lipossarcoma. Bloodwork showed: glucose 58 (76-115) mg/dl, C peptide 0.10 (1.10 – 4.40) ng/ml, insulin <0.40 (2.6-24.9) U/ml and IGF1 30.1 (67.0-195) ng/ml. Due to a laboratorial mistake, IGF2 was not measured. However, after mass excision, bloodwork showed normal IGF1 [220 (67.0-195) ng/ml], C peptide [2.30 (1.1-5.0) ng/ml] and insulin [8.35 (2.6-24.9) uUI/ml] values, and so IGF2 tumor production was assumed. After surgery, no further hypoglycemia events were detected.
Conclusão
NICTH must be considered, even when IGF2 measurement isn't possible, in the presence of low glucose values and suppressed C peptide/insulin and IGF1 values.

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Increased frequency of breast cancer in young Carney Complex patients suggests a role for inactivation of the tumor suppressor gene PRKAR1A

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Objective
Carney Complex (CNC) is a rare hereditary genetic syndrome, mostly due to inactivating pathogenic variants of the tumor suppressor gene *PRKAR1A*. It has a wide spectrum of manifestations with frequent pigmented skin lesions, cardiac myxomas, primary pigmented nodular adrenocortical dysplasia, acromegaly and thyroid cancers. Breast benign tumors (fibroadenomas, ductal adenomas and myxoid lesions) have been associated with CNC, but so far, association with malignancy has not been investigated.
Methods
The present study was designed to describe the characteristics of breast tumors diagnosed in CNC patients and their association with other manifestations of CNC and *PRKAR1A* genotype. Since breast cancer is the most frequent cancer in women, malignant breast lesions were carefully analyzed. This cohort comes from a 3 years' follow-up multicenter French prospective study of CNC patients (Espiard, JCEM 2020). The 50 included women were investigated for CNC manifestations and particularly breast tumors, with breast echography, genetic and hormonal investigations, in order to characterize them and assess the frequency and average age of breast cancer.
Results
Among the 38 women with breast imaging, 14 had breast tumors (50% bilateral). Ten women (20%) presented with benign tumors. Six women presented (12%) with breast carcinomas: five had invasive cancer under 50 years of age (4 ductal adenocarcinomas and one solid intracystic papillary carcinoma) and one had ductal carcinoma *in situ.* The occurrence of breast cancer was more frequent in the CNC women with *PRKAR1A* pathogenic variants than in the general population (OR = 6.2[1.58-17.31]; $P = 0.006$). The mean age at breast cancer diagnosis was 44.7 years old, 17 years younger than in the general population. Cumulative risk of developing breast cancer in our cohort was higher if compared to French women under 40 (OR = 30.25[6.06-93.06]; $P = 1{,}67^{-4}$) or 50 years old (OR = 116,90[19,14-1246,78]; $P = 8{,}17^{-8}$). Breast cancer had good prognosis factors: 5 out of 6 tumors were T1N0M0. One woman had metastatic breast cancer, alive after 15 years follow up. All breast cancers were negative for HER2, with positivity for estrogen receptor(100%) and progesterone receptor(50%). They all occurred in individuals with familial CNC and *PRKAR1A* pathogenic variants. Loss of heterozygosity at the *PRKAR1A* locus observed in 2 investigated breast carcinomas tissues suggests that *PRKAR1A* bi-allelic inactivation could promote breast cancer development.
Conclusions
Breast carcinoma occurs frequently and prematurely in women with CNC, suggesting that CNC predisposes to breast carcinoma. This suggests that adequate screening strategy (starting around 40 years old) and follow up should be discussed in CNC women.

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P661

Revealing the anti-cancer region within KL1 subunit of the hormone klotho

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Background
Klotho is a 1012 amino acids transmembrane protein, composed of two internal repeats, KL1 and KL2, that can be cleaved, shed and act as a circulating hormone. Klotho regulates several pathways, including fibroblast growth factor 23 (FGF23), Wnt-β/catenin and the cation channels TRPV and TRPC. Our group and other labs identified klotho as a potent tumor suppressor in breast and pancreatic cancers and that KL1 domain is responsible for this activity. Yet, the mechanism mediating this activity remains unresolved.
Aim
Reveal the role of C-terminal and N-terminal parts within KL1 and understand their association to the tumor suppressor activity.
Methods
Expression vectors of truncated KL1 included C-terminal truncations: KL340, KL320, and N-terminal truncation: KL88-340. We assessed their anti-cancer activity or regulation of the Wnt-β/catenin pathway by colony formation assay and co-expression in cancer cells. We used MCF-7, MDA-MB-231, PANC1, MIAPaca-2, HCT116. We then performed RNA seq analysis on MCF7 cells over-expressing either KL1 or one of the C-terminal truncated KL340, KL320 to decipher global transcriptome differences.
Results
Over expression of C-terminal truncated protein KL340 inhibited colony formation, unlike KL320 in pancreatic and colon cancer. In breast cancer KL340 partially inhibited colony formation. N-terminal truncated proteins lost the ability to inhibit colony formation. Investigation of the Wnt-β/catenin signaling showed that only KL1 and KL340 decreased the levels of wnt3a in all cancer cell lines. Gene expression profile in MCF7 cells overexpressing KL1 and KL340 reflected their tumor suppressor activity.
Conclusions
This study reveals that klotho's anti-cancer effect may be mediated by an N-terminal sequence. KL340 is the shortest truncation that retains the significant tumor suppressor activity of KL1. KL340 and KL1 induce a wide systemic transcriptome change in breast cancer, affecting cell survival. The structural features of the protein gained by the N-terminus remains questionable. Moreover, the 20 amino acids missing in KL320 compared to KL340 are critical for the tumor suppressor function and require further investigation.

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P662

Vision-related Quality of Life in Patients with Childhood-onset craniopharyngioma – Results of HIT-Endo and KRANIOPHARYN-GEOM 2000/2007

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Background
Quality of life (QoL) has become a critical component of therapeutic outcomes in the survivors of childhood-onset craniopharyngioma (CP). Visual deficiency adversely affects daily functioning and QoL in childhood CP. This cohort study aimed to report the vision-related QoL in CP patients.
Methods
120 patients with CP were included in this study and prospectively observed. The primary outcome measure was pediatric QoL (PEDQOL score) in patients with and without visual impairment from presentation at the time of CP diagnosis to three-year follow-up. Potential risk factors associated with visual impairment were analyzed using multivariable logistic regression.
Results
The most common presenting symptoms at the time of CP diagnosis were headache (42%), visual impairment (20%), and growth retardation (12%). Visual impairment was found in 87 patients (70%). Ophthalmologic examination and PEDQOL scores, which were grouped into seven domains: physical functioning, cognition, social functioning friends, social functioning family, and body image, were evaluated at the third month, first-year, and third-year after diagnosis. Parents of children with visual impairment report worse social functioning in their families than parents of children without visual impairment, one ($P=0.017$) and three years ($P=0.011$) after diagnosis. After three years, children with visual impairment were found to have worse quality of life in the autonomy domain of self- ($P=0.029$) and parental assessment ($P=0.048$). High tumor volume (>21 cm^3), radiation therapy and extrasellar tumor location were identified as potential risk factors for visual impairment.
Conclusions
We conclude that visual impairment has a negative impact on QoL after CP. Early detection of visual impairment, regular QoL assessment, and risk-appropriate follow-up care are recommended.

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P663

High diagnostic yield of multigene panel testing in patients with endocrine tumors

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Hereditary genetic variants are common among patients with endocrine tumours. Some specific clinical conditions are informative for certain monogenic syndromes (i.e., Carney complex, MEN1, MEN2, von Hippel Lindau syndrome) but manifestations characteristic for these syndromes occur more commonly as apparently sporadic. Other tumours, i.e., pheochromocytoma/paragangliomas (PPGL) are linked to multiple genes, hence a multigene approach in molecular genetic testing strategy is recommended. As a national reference centre for molecular genetic testing of patients with hereditary cancer, we prospectively tested a multigene panel's diagnostic utility which covers 113 genes associated with various tumours. The most common genes responsible for hereditary endocrine tumours are also included in this panel. Between October 2021 and December 2022, we analysed 97 patients as part of their routine clinical and molecular genetic diagnostic workup. All pathogenic/likely pathogenic variants with unknown significance were validated from a second DNA sample using gold-standard Sanger sequencing or multiplex ligation-dependent probe amplification. Patients with primary hyperparathyroidism, gastro-pancreatic neuroendocrine tumours, pheochromocytoma, paraganglioma, adrenocortical cancer, medullary thyroid cancer, neurofibromatosis, etc. were referred for testing. Of 97 patients, in 24 cases the relevant P/lP variants were identified (24/97; 25%). Of these, the most common variants were detected in *MEN1, SDHx*, and *NF1* genes. In 8 cases secondary findings were reported in *BRCA2, ATM, CHEK2, MSH6* and *NF1* genes (8/96; 8%). Our data show that using a comprehensive multigene panel as a routine diagnostic tool for testing patients with endocrine tumours yields a high diagnostic benefit in a short turnaround time. Incidentally identified variants may serve as a potential therapeutic target (such as *BRCA2* or *MSH6*) in tumours where therapeutic possibilities are limited (i.e., adrenocortical cancer).

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Mutational profiles of typical and atypical bronchial carcinoids

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Introduction
Typical and Atypical bronchial carcinoids (TBC and ABC) are rare neuroendocrine neoplasms (NEN). TBC are low grade and well-differentiated NEN often with indolent clinical behavior, slow growth, rare extra-thoracic metastases, and with a long survival following surgical resection. Conversely, ABC have often a worse prognosis with a greater tendency to metastasize and recur. A better understanding of TBC and ABC genetic background would help in evaluating prognosis, especially in advanced BC resistant to treatment.
Aim
Investigate by whole-genome sequencing the mutational profile in TBC vs. ABC using a multigenic panel previously employed in pancreatic NEN.
Materials and methods
Genomic DNA was isolated from 25 TBC and 13 ABCs frozen samples. 11 genes (MEN1, DAXX, ATRX, MUTYH, SETD2, DEPDC5, TSC2, ARID1A, CHECK2, MTOR, PTEN) were sequenced by Next Generation Sequencing (NGS).
Results
TBC more frequently presented alterations vs. ABC in TSC2, ARID1A and DEPDC5 genes (OR 5.4, 3.7 and 3.7, respectively). Specifically, 32% of TBC

samples showed alterations in the DUF3384 domain of TSC2 gene, 24% in ARID1A and/or DEPDC5 genes. TSC2, ARID1A and DEPDC5 were altered in 8% of ABC samples, respectively.
Conclusions
The present study suggests that TBC are more frequently mutated in TSC2, ARID1A and DEPDC5 genes as compared to ABC. Interestingly, preliminary studies indicate that TGF-B and mTOR crosstalk might contribute to resistance to everolimus (an mTOR inhibitor) in advanced TBC, which might be explained by altered TSC2 gene (involved in mTOR signalling) in our study. In light of these findings, further studies with larger and balanced groups are needed to confirm these observations and to investigate the clinical significance of these mutations in TBC and ABC, as well as to explore the potential therapeutic implications of targeting TSC2 and other genes identified in our study in TBC and ABC.

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P665

A rare cause of bilateral adrenal masses

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Introduction
Bilateral adrenal masses may appear in the context of metastatic disease, adrenal congenital hyperplasia, primary tumors or infections, among others. Primary adrenal lymphoma is rare, accounting for approximately 1% of cases of non-Hodgkin lymphoma.
Clinical case
47-year-old woman, with a history of *erythema nodosum* and left hemithyroidectomy in the context of benign nodular disease. She presented with persistent fever and tiredness. An abdominal ultrasound showed bilateral adrenal nodular lesions. An abdominal CT confirmed the presence of bilateral adrenal masses, the one on the right with 129x63mm and the one the left with 113x63mm, with relative and absolute washouts of 16% and 40%, respectively. Suspicious retroperitoneal adenopathies were also present. The patient presented no signs or symptoms suggestive of pheochromocytoma, hypercortisolism or hyperandrogenism and physical examination showed cutaneous hyperpigmentation. Bloodwork revealed: ACTH 1964 (7.2-63.3) pg/ml, plasma cortisol 6.03 (5.0-25.0) ug/dl, immeasurable levels of testosterone and estradiol, DHEA-S 3.16 (35-256) ug/dl, and normal urinary metanephrines and 17-OH progesterone. She started therapy with 20mg of hydrocortisone daily. In order to study the possibility of adrenal metastasis of a primary occult tumor, an 18F-FDP-PET/CT was performed, that showed bilateral malignant involvement of the adrenal glands as well as pelvic and axillary lymph node metastasis. Given the absence of a primary occult tumor and hormonal hypersecretion, and taking into account the rarity of bilateral adrenal carcinomas, primary adrenal lymphoma presented as a possible diagnosis. Additional bloodwork showed elevated β2-microglobulin [6.03 (<3) ug/dl], LDH [421 (67-248) U/l] and ferritin [293 (10-120) ug/l]. A left adrenal biopsy confirmed the diagnosis of large cell diffuse B lymphoma. The patient was started on chemotherapy, with significant improvement.
Conclusions
Although rare, adrenal lymphoma, whether primary or secondary, must be thought of as a possible diagnosis in the presence of bilateral adrenal masses with suspicious characteristics on imaging studies. Clinical and analytical evaluation is essential.

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P666

A rare case of immunotherapy related adrenalitis

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Introduction
Immunotherapy has transformed the outcomes of various cancers. Monoclonal antibodies against cytotoxic T lymphocyte antigen 4 (CTLA4), programmed cell death 1 (PD1) and its ligand, PDL1 target mainly T cells, unleashing the immune system against tumour cells. Immune checkpoint inhibitor therapy results in a variety of immune related adverse events, including various endocrinopathies. Thyroid disorders, pituitary disorders are relatively more common compared to primary adrenal insufficiency and diabetes mellitus. Immune therapy related primary adrenal insufficiency is rare and can present acutely. Its incidence ranges from 1 to 2 % with monotherapy to 5 to 8 % with combination regimens. Presenting symptoms are usually like secondary adrenal insufficiency or can be completely nonspecific. We present a rare case of primary adrenal insufficiency caused by combination immunotherapy.
Case Presentation
A 72-year-old male with a history of hypertension, Type 2 Diabetes and Atrial fibrillation was treated with combination ipilimumab and nivolumab for metastatic melanoma. Following the second cycle, he developed immune-checkpoint inhibitor (ICPi) induced dermatitis which was treated with high dose glucocorticoids (which were subsequently weaned off) and ICPi treatment was held for 2 months. Following cycle 3, the patient developed acute kidney injury which improved with oral glucocorticoid but there was persistent hyperkalaemia which was disproportionate to the creatinine. The patient's cortisol was unremarkable [444 nmol/l] and due to the ongoing hyperkalaemia, he was commenced on mycophenolate mofetil. He was also treated with sodium zirconium and sodium bicarbonate for the ongoing hyperkalaemia. As an investigative screen renin 19.5 nmol/l(0.3-2.2), aldosterone <50 pmol/l(0-630), sodium (130 mmol/l) and potassium (7.1 mmol/l) were in keeping with hyper-reninaemic hypoaldosteronism. His urea (10 mmol/l), creatinine (117 umol/l) were disproportionate to the electrolyte imbalance, but he maintained satisfactory random cortisol readings of 314 nmol/l. Treated with fludrocortisone which resulted in normalisation of the potassium. Two months later he had further screening bloods and his cortisol was undetectable. He was referred to endocrinology where hydrocortisone was added to his therapy. His ACTH was markedly raised at a value of 1009 ng/l (0-46) in keeping with ICPi-induced adrenalitis and Adrenal antibodies were negative. In retrospect, it was felt that his mineralocorticoid deficiency preceded the glucocorticoid deficiency by at least 2 months representing an earlier presentation of adrenalitis. Clinicians should be aware of the possibility of ICPi-induced adrenalitis in patients who present with refractory hyperkalaemia and hyponatraemia, even in the setting of a normal cortisol measurement.

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Multidisciplinary Management of Paragangliomas in a Reference Unit Hospital in Spain

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Introduction
Paragangliomas and pheochromocytomas (PGGs) are infrequent tumors of the autonomic nervous system that represent a diagnostic and therapeutic challenge. Management and follow-up of PGGs requires specialized knowledge and solid experience, which, given the rarity of these diseases, is available only in highly specialized centers. University Hospital La Fe (Spain) was designated a reference unit on Neuroendocrine Tumors by local sanitary authorities in 2018. The aim of this study is to describe multidisciplinary management of PGGs in our center from Nov 2021-Nov 2022.
Material and Methods
Descriptive and unicentric study that includes 173 patients with PGG evaluated at Hospital Universitari i Politècnic La Fe in Valencia, Spain.
Results
173 patients have been evaluated (27 pediatric age) during the period november 2021-2022, 27 of them in a first evaluation. Mean adult age at visit 45.6 years (SD). 66% ($n=114$) of the totality of patients were known germline mutation carriers: 28% MEN 2A, 22% SDHD, 27% SDHB, 3.5% SDHA, 1.7% SDHC, 9.7% VHL, 2.6% FH, 3.5% MEN 2B, MAX 0,5% and 1.7% NF1. 43 (24.8%) were mutation carriers non-affected and 14 (8%) had metastatic disease. During this year all of the patients have been followed in the Endocrinology department (adult or pediatrics), 48%($n=83$) of the patients have required follow-up from more than one speciality. Patients have required evaluation during this year by the following specialists: Oncology 14 (8%), Endocrine Surgery 10 (7.5%), Pediatric Surgery 2 (1.1%), Head-neck surgeon 44 (25.4%), Radiotherapy 16 (9.2%). A

new diagnosis of PGG tumor was made in 26 patients. All patients have performed urine catecholamine and metanephrine analyses, and 17% were functioning tumors. Imaging tools have included: 27 total body MRI, 30 head-neck MRI, 18 abdominal MRI, 60 PET/CT 68Ga-DOTATOC, 11 123-I-MIBG, 3 PET/CT 18F-DOPA, 56 PET/CT 18F-FDG. Surgical procedures during this period included: 10 adrenalectomies, 8 head and neck surgeries, 1 complex peritoneal surgery of PGG implants. 9 patients required presurgical medication with alpha and beta blockade. Nuclear medicine treatment included: 5 I131-MIBG and 3 Lu-DOTA-TATE. Other treatments include: 4 radiotherapy, 2 chemotherapy and 10 others.

Conclusions

All patients with PGG must be followed by the Endocrinology department following current clinical guidelines. Patients with PGG often require evaluation by more than one specialist and require multidisciplinary management in highly specialized centers which offer surgical, medical and imaging technique expertise.

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MEN1 and Liposarcomas: Report of three cases

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Introduction

Multiple endocrine neoplasia type 1 is a rare inherited tumor syndrome defined most frequently by the association of primary hyperparathyroidism, gastro-entero-pancreatic tract endocrine neoplasia and anterior pituitary gland adenoma and less commonly by neuroendocrine tumor of the adrenal cortex, thymus and bronchis. Association to non-endocrine tumors affecting the skin, glial cell, smooth muscle or breast cancer has been described. As far as we know, only one case of liposarcoma associated with MEN1 has been reported. Herein, we report data from the French MEN-1 Register showing 3 cases of liposarcoma.

Case 1

Male patient born in 1973.

-Personal medical history:Removal of a cervical lipoma.

-2001:Surgery for a **well differentiated liposarcoma** of the left hip that was growing gradually for years.

-2007:Genetic diagnosis of **MEN1** (Father with MEN1).

-2015:Subtotal parathyroidectomy after a **primary hyperparathyroidism** known since 2007.

The histological analysis found an aspect of hyperplasia with predominance of clear cells and presence of oncocytic foci, no suggestive sign of malignancy.

-2014:Ulcerative duodenitis due to **Zollinger-Ellison Syndrom**.

-2016:Right middle lobectomy for a **very well-differentiated neuroendocrine carcinoma**. Immunohistochmistry testing:Synaptophysin+, Chromogramine A+, TTF1-, Ki67<3%.

-No new tumor(pancreatic, pituitary, etc) at the last follow-up.

Case 2

Male patient born in 1937.

-Family history of MEN1.

-2005: **Primary hyperparathyroidism** treated by Subtotal parathyroidectomy(-hyperplasia), removal of the fat tissue surrounding the left thymic horn and right thyroid lobectomy. **Confirmation of MEN1 germline mutation**.

-No MRI was performed because of claustrophobia. Normal pituitary gland function.

-August 2011:Weight loss and asthenia revealing a 16cm **well differentiated retroperitoneal liposarcoma** after a distal pancreatectomy, a splenectomy and a splenic flexure colectomy was performed. Discovery at the same time of a **pancreatic well-differentiate endocrine tumor** and a stomach stromal tumor.

-July2012:Local and regional recurrence(lung, pleura, liver).

Case 3

Female patient born in 1944 carrying a **MEN1 mutation**.

-1990: **Primary hyperparathyroidism** initially treated by a resection of the two lower parathyroid in 1990 then by a complete parathyroidectomy(Hyperplasia) followed by a parathyroid gland reimplantation on the left arm in 1994.

-2004:Distal spleno-pancreatectomy(**Well-differentiated pancreatic neuro-endocrine tumor**) and left adrenalectomy(Hyperplasia).

-2010:Discovery of lower-grade astrocytoma. Unremarkable pituitary MRI.

-2012:Quick appearance in 3 weeks of a tumor on the rooth of the left thigh. The biopsy showed an **undifferentiated pleomorphic liposarcoma** stage II.

Conclusion

These 3 cases from the French MEN-1 Register(1570 cases) show that liposarcoma is not rare within MEN1 population compared to the general population (1/100000 person/year). Thus the association of the two entities may not be fortuitous. Further research is warranted and more cases are needed to establish that liposarcoma might be a new tumor type in patients with MEN1.

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P669

Clinical findings, treatment modality and outcomes of adrenocortical carcinoma: a retrospective review of single tertiary center experience

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Background & Aim

Adrenocortical carcinoma (ACC) is an extremely rare malignancy usually with poor outcomes, although the prognosis varies greatly depending on the initial tumor stage. Here we present clinical and outcome diversity of the patients in a single center.

Methods

We retrospectively analyzed 16 patients with ACC diagnosed between 2000 and 2022. Demographical findings, hormonal status, radiological findings, ENSAT stage, weiss score and Ki67 levels, multidisciplinary treatment modalities and prognostic outcomes were evaluated.

Results

There were 8 (50%) women and men with a mean age of 56 (±12) years. Mean follow-up was 88 (±66) months, 11 (69%) patients were still alive without any metastasis and local recurrence. 5 patients died during follow-up, 4 of them were due to disease progression however one patient with complete remission were died due to myocardial infarction. Disease specific mortality was 25% with a mean survival of 69 months of these four patients. 25% of the patients were hormonally active predominantly hypercortisolism. The mean tumor size was 93.5±56.8 mm (range, 30-250 mm), 3 (18%) patients had local invasion and 3(18%) patients had distant metastasis including thorax, bone and liver metastasis. 16 patients (94%) underwent surgery, 5 of them had laparoscopic adrenalectomy, 2 patients had also metastasectomy and lymphnode dissection. Postoperative pathology revealed 4 (25%) oncocytic, 2 (12,5%) sarcomatoid, 2 (12,5%) mixoid and 8 (50%) clasiccal subtype ACC. 4 (25%) patients had venous and 12 (75%) had capsule invasion, mean Ki 67 score was 16 (range,2-90). According to ENSAT staging, two (12,5%) patients were stage 1, nine (56%) patients were stage 2, one was stage 3 and four (25%) were stage 4 disease. Six patients had adjuvant mitotane treatment and two patients had mitotane and EDP treatment. 2 of 6 patients on mitotane treatment had disease progression and added on EDP treatment. 2/6 patients were still on adjuvant mitotane and remaining 2/6 had remission and treatment stopped. All patients had drug toxicities in variable levels, majority of them were mild GIS symptoms and liver function test alterations, however one patient had moderate dermatological toxicity and one had neurologic toxicity necessitating dose decrement but recovered without any sequelae.

Conclusion

ACC has wide range of clinical course; therefore ACC management has to be patient specific. Mitotane is an effective treatment in properly selected patients and may be a curative treatment. Careful monitoring is mandatory to achieve disease control.

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Incidental Metastases of Medullary Thyroid Carcinoma in a Patient with Multiple Endocrine Neoplasia Type

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Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a rare hereditary tumour syndrome inherited in an autosomal dominant manner and characterized by a predisposition to a multitude of endocrine neoplasms primarily of parathyroid, enteropancreatic, and anterior pituitary origin, as well as nonendocrine neoplasms. However, thyroid cancer is not part of this syndrome.

Case details
We report the case of a 36-year-old man diagnosed with primary hyperparathyroidism after being referred for mild asymptomatic hypercalcemia. Genetic testing for MEN1, CDKN1B, CDC73 and CASR were requested and an heterozygous variant c.415C>T (p.His139Tyr) classified as pathogenic variant of MEN1 in ClinVar database was detected. The patient underwent subtotal parathyroidectomy and removal of the entire thyrothymic space. The pathology report confirmed three parathyroid glands compatible with hyperplasia and thymic remains. In addition, two of the three incidentally excised nodes were reported as microscopic metastases from medullary thyroid cancer (MTC) based on their morphologic and immunohistochemical profile (positive for CKPan and calcitonin). Serum chromogranin A and calcitonin were normal. After confirming that 24-h urine catecholamines and metanephrines were normal, total thyroidectomy and prophylactic central-compartment neck dissection were performed. The pathology study showed focal parafollicular cell hyperplasia without histological findings of malignancy and ruled out additional nodal metastasis. An additional molecular genetic study of the RET proto-oncogene ruled out germline mutations. Thoracoabdominal CT and hepatic MRI showed new findings of MEN1 related-conditions such as numerous millimetric hypervascular pancreatic nodules in head, body and tail, as well as one adrenal lesion of 16x15 cm with radiological characteristics of adenoma. A 68Ga-DOTATOC PET was ordered and pancreatic foci of pathological overexpression of somatostatin receptors were confirmed, but no other foci suggestive of possible metastasis from MTC. Additional hormonal studies ruled out secretory activity of both pancreatic and adrenal lesions, and a pituitary MRI was normal.
Conclusions
To best of knowledge this is the first case reported in the literature of a patient with MEN1 who has been affected by a concomitant MTC.

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Environmental Endocrinology

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Assessment of oxidative stress, neurotoxicity, genotoxicity and prey-predator interactions in freshwater snails exposed to microplastics

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Microplastics are one of the major pollutants over the globe jeopardising the health of aquatic life. The ecotoxicological effects of microplastics are well investigated in marine organisms, however, their impact on freshwater ecosystem remain unnoticed. Gastropod molluscs serve as good bioindicators for environmental toxicology. Therefore, we studied two commonly found freshwater snails, *Lymnaea acuminata* and *Indoplanorbis exustus* and checked the effect of microplastics obtained from 3 polymers; polypropylene, polystyrene and polyvinyl chloride. The aim of our study was to prepare microplastics, their characterization and to examine the oxidative damage caused by them. Also, the neurotoxicity and genotoxicity caused due to microplastics were assessed. The behavioural assay was performed to scrutinize the predator-prey interactions. Lipid peroxidation levels, catalase activity and superoxide dismutase activity were elevated in the intestine and ovotestis after microplastic exposure. It was found that, polypropylene caused less oxidative damage than polystyrene, while, highest damage was caused by polyvinyl chloride. Acetylcholinesterase (AChE) inhibition and DNA damage was maximum in polyvinyl chloride exposure as compared to polypropylene and polystyrene. Variations in the antioxidant enzyme level, acetylcholinesterase activities and DNA damage are indicative of oxidative stress, neurotoxicity and genotoxicity in snails. Microplastic exposure also disrupted their ability to detect the presence of predator in their surroundings. Physiological and behavioural parameters of these organisms can reveal the consequences of environmental toxicity.

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P128

Thyroid cancer diagnostics related to occupational and environmental risk factors: an integrated risk assessment approach

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There are still many questions remaining about the etiopathogenesis of thyroid cancer, themost common type of endocrine neoplasia. Numerous occupational and environmental exposureshave been shown to represent important risk factors that increase its incidence. Updated informationabout thyroid cancer diagnostics related to occupational and environmental risk factors is reviewedhere, considering an integrated risk assessment approach; new data concerning thyroid canceretiology and pathogenesis mechanisms, diagnostic biomarkers and methodologies, and risk factorsinvolved in its pathogenesis are presented. A special emphasis is dedicated to specific occupationalrisk factors and to the association between environmental risk agents and thyroid cancer development.The occupational environment is taken into consideration, i.e., the current workplace and previousjobs, as well as data regarding risk factors, e.g., age, gender, family history, lifestyle, use of chemicals,or radiation exposure outside the workplace. Finally, an integrative approach is presented, underlyingthe need for an accurate Risk Assessment Matrix based on a systematic questionnaire. We proposea complex experimental design that contains different inclusion and exclusion criteria for patientgroups, detailed working protocols for achieving coherent and sustainable, well-defined researchstages from sample collection to the identification of biomarkers, with correlations between specificoncometabolites integrated into the Risk Assessment Matrix.

Keywords
Thyroid cancer diagnosis; occupational risk; environmental risk factors; oncometabolites; risk assessment matrix

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P399

Tributyltin exposure during gestation and lactation changes the hormone profile of the offspring in a sex- and age-dependent manner

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The ingestion of marine foods is a potential route of contamination by tributyltin (TBT), a biocide organotin used as an antifouling in boat paints. TBT causes a phenomenon known as imposex, that induces, for instance, the irreversible appearance of male sexual characteristics in gastropod females. In mammals, TBT also directly impairs the sexual development. In fact, it is known that TBT can affect women in reproductive age. Our aim was to study whether the maternal exposure to TBT, in a high dose, during pregnancy and lactation can cause long-term hormonal dysfunctions in male and female offspring. Experimental design was approved by the Ethics Committee (protocol: CEUA/010/2019). Wistar rats were mated and after pregnancy detection, females were randomly separated into 2 groups: dams received vehicle (0.1% ethanol; Control group) or TBT (1000 ng/kg of body weight, bw). Exposure occured from the 7th gestational day until the end of lactation (21 days of lactation period) by gavage. We evaluated plasma hormones of male and female offspring at puberty (45 days old) and adulthood (180 days old) by enzyme-linked immunosorbent assay (ELISA). Data were analyzed by Student's t test ($n=7$/group). During puberty, male TBT offspring showed a significant reduction of plasma follicle stimulating hormone (FSH) (-42%), luteinizing hormone (LH) (-51%), testosterone (-70%), estradiol (-39%), insulin (-30%) and corticosterone (-78%) levels. No differences were observed in plasma thyroid-stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3) and leptin. Female TBT offspring presented increase in plasma testosterone and reduction of corticosterone levels (2-fold and -43%, respectively), without changes of other hormones. On the other hand, at adulthood, TBT males displayed higher plasma T3 (2.7-fold), insulin (1.8-fold), corticosterone (3.8-fold) and leptin (+56%) levels when compared to control ones. Adult TBT females only displayed lower plasma corticosterone level (-45%). Taken togheter our data indicate that perinatal exposure to TBT causes endocrine dysfunctions during puberty period and adult life. Interestingly, in this model we evidence a sex dimorphism, since male offspring seem to be more affected than females.

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P400

Endocrine disrupting chemicals and thyroid hormone patterns during gestational periods: a systematic review approach

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The Hypothalamic Pituitary Thyroid (HPT) axis is well-known as a classic endocrine negative feedback loop: increased levels of thyroxine (T4) in the blood are associated with a reduction of thyroid stimulating hormone (TSH) production and vice versa. However, the thyroid hormone (TH) system is sensitive to alterations by a number of endocrine disrupting chemicals (EDCs). Intriguingly, exposure to specific EDCs can decrease the levels of T4 but this might be not followed by the expected increase of TSH. The reasons for such patterns are still unclear. The aim of the present evidence mapping was to obtain a comprehensive picture of T4/TSH patterns evoked by EDC exposures in rodent models. We conducted an extensive systematic literature search of peer-reviewed articles in which we collected studies that met the following criteria: experimental data (T4, TSH) for rodent models (pups and/or dams) exposed during perinatal periods through the diet to different chemical doses. Our results show that the idealized view of the HPT axis is not supported by the evidence when EDCs are involved. When administered during gestation, some EDCs induced reductions of T4 serum levels in pups followed by increased TSH levels. These chemicals often disrupted the synthesis of THs and the hepatic metabolism. However, with others, the expected TSH increase did not materialise, and these chemicals often interfered with the removal of T4 via up-regulated conjugating enzyme systems in the liver.
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P671

Maternal caffeine intake at low doses causes hormonal and metabolic changes in the offspring in a sex-dependent manner

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Caffeine crosses the placenta and mammary barrier and can affect the offspring metabolism and endocrine system from heavy caffeine users. Here, we tested the impact of a safe dose of maternal caffeine (200-300 mg/day) on plasma hormone of offspring from both sexes at different ages (weaning, puberty and adulthood). For this, pregnant Wistar rats received caffeine (25mg/kg/day) by gavage or vehicle during gestation (GEST group), lactation (LACT group) or both periods (G + L group). Litters were adjusted to 8 pups per dam. Biometric parameters were recorded in dams and offspring. Milk was collected at weaning. Oral glucose tolerance test (OGTT) was performed in offspring at postnatal (PN) days 45 and 180; hormones were measured at PN21 and PN180 by ELISA. Data were analyzed using one way ANOVA followed by the Newman-Keuls post-test (Ethical committee 26/2019). At delivery, dams of GEST and G + L groups showed lower food intake and body weight (-18% and -12%; respectively, $P < 0.05$). At the end of lactation, all dams' caffeine groups had no change of leptin and insulin in plasma and milk; showed lower plasma total T3 (GEST = -70%, LACT = -52% and G + L = -56%; $P < 0.05$), although no differences of free T4 and TSH. Regarding the offspring at birth, only GEST and G + L females showed lower body weight (-6%; $P < 0.05$). At weaning, all males' caffeine groups showed lower T3 (G = -75%, LACT = -80% and G + L = -58%; $P < 0.05$), without changes of T4 or TSH, while females had no changes of these hormones. At weaning, G + L females presented hyperinsulinemia (+100%; $P < 0.05$) despite normoglycemia. From weaning until adult life, GEST and G + L females showed lower body weight (-6%; $P < 0.05$), whereas GEST and LACT males had higher body weight (+6%; $P < 0.05$). At puberty, only LACT females showed hyperglycemia at 30 and 120 minutes after glucose overload, characterizing a glucose intolerance. At adulthood, GEST and LACT females displayed glucose intolerance. Males had no differences in glycemia in the OGTT at PN45 and PN180. Plasma insulin, leptin, T3 and T4, TSH and estradiol were not altered in adult female offspring. However, plasma testosterone was higher in LACT females (+152% $P < 0.05$). Adult male offspring from all caffeine groups did not show changes of these hormones. We suggested that perinatal caffeine exposure, even at a safe dose, induces short- and long-term hormonal changes and metabolic disturbances in offspring especially in females. Thus, during the critical periods of pregnancy and breastfeeding, the consumption of caffeinated beverages and foods should be avoided.

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Pituitary and Neuroendocrinology

P129

Asymptomatic Familial Hyperprolactinemia Caused by a Unique bi-Allelic Variant in the Prolactin-Receptor Gene

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Introduction
Hyperprolactinemia is usually an acquired condition. Typical clinical manifestations include hypogonadism, infertility, and galactorrhea. Rarely, hyperprolactinemia has been attributed to a variant in the prolactin receptor gene (*PRLR),* presenting as agalactia, without hypogonadism, infertility, or galactorrhea.
Aim
In the current study we aimed to delineate the clinical phenotype and the genetic basis of marked hyperprolactinemia found in few females from one large kindred.
Methods
We have ascertained extended inbred kindred with multiple female subjects displaying presumably asymptomatic hyperprolactinemia. The family members underwent clinical, laboratory and imaging assessment. Whole exome sequencing has been used to obtain genetic molecular diagnosis of the proband. Segregation analysis was performed by Sanger sequencing.
Results
Fourteen family members, 7 females and 7 males of 3 different branches and of 2 generations were evaluated. Ethylene glycol precipitation and pituitary Magnetic Resonance Imaging revealed no evidence of macroprolactin or pituitary adenoma, respectively. Four females of reproductive age with elevated prolactin levels (X6-10 of the upper limit of norm), harbored a homozygous PRLR(NM_000949.7):c.1750del (p.Glu584AsnfsTer49) variant, predicted to change the amino acid (aa) sequence of the last 39 aa of the encoded PRLR, elongating it by additional 13 aa, thereby affecting its intracellular domain. All 4 had regular ovulatory cycles and no galactorrhea. Of these, 3 homozygous females conceived spontaneously. Of 3 who gave birth, only one nursed without difficulties, while 2 reported "lack of milk' and did not have breast engorgement after stopping breastfeeding. All three postmenopausal women (one homozygous, one heterozygous, and one wildtype of the *PRLR* gene) had prolactin levels within the normal range. However, the homozygous postmenopausal woman had prolactin level X2 of ULN at menopause transition. She had 5 spontaneous pregnancies and successfully nursed all her children. All seven males (2 homozygous and 5 heterozygous) had prolactin level within the normal range and did not demonstrate any signs or symptoms related to hyperprolactinemia.
Conclusions
We describe a novel homozygous *PRLR* p.Glu584AsnfsTer49 variant predicted to affect the intracellular domain of the PRLR, resulting in significant, apparently asymptomatic hyperprolactinemia among females in their reproductive age, with a possible mild lactation difficulty. It might be suggested that the hyperprolactinemia largely compensate for the lower activity or stability of the PRLR.

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P130

Increased Plasma Leptin and Agouti-Related Peptide May Be Related To Sleep Alterations In Patients With Active Cushing's Syndrome

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Aim
To evaluate sleep architecture of patients with Cushing's disease (CD) and to explore whether agouti-related peptide (AgRP) leptin, and interleukin-6 (IL-6) play a permissive role in sleep alterations.

Methods
We performed polysomnography on 26 patients with active CD and age 26 age- and sex-matched control subjects. Blood samples were obtained from all participants for the analyses of AgRP, leptin, and IL-6. The laboratory and sleep-related parameters were compared.
Results
The groups were similar in age, gender, and body mass index. Plasma AgRP (13.2±7.4 pg/ml vs 9±3.1, $P=0.029$), leptin (59.5 mg/l, [IQR] 32.6-94.6)vs 25.3 mg/l, [IQR] 12.9-57.5, $P=0.007$) and IL-6 levels (1.2 pg/ml, [IQR] 0.5-2.7 vs 0.6 pg/ml, [IQR] 0.5-2.7, $P=0.058$) were higher in CD group. The CD group had reduced sleep efficiency (71.6±12.1% vs 78.8±12.6%, $P=0.042$) and increased wake after sleep onset % (WASO%) (24.7±13.1% vs. 17.4±11.6%, $P=0.040$) as compared to control group. AgRP and leptin correlated negatively with total sleep time, sleep efficiency, N2%, and positively with WASO%. In multiple regression analyses, AgRP emerged as a significant predictor of sleep efficiency ($\beta=0.481$ and $P<0.05$) and WASO% ($\beta=0.452$ and $P<0.05$) among other confounders. Seventeen patients with CD and 18 control subjects had obstructive sleep apnea (OSAS).
Conclusion
Active CD hampers sleep efficiency and continuity which may be associated with increased plasma AgRP. Leptin may correlate negatively with sleep efficiency and continuity. More than half of patients with CD may suffer from OSAS. Therefore, patients with CD who complain of impaired sleep or have symptoms attributable to OSAS should undergo polysomnographic evaluation.

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P131

Somatostatin receptor expression in pituitary tumours according to the 2022 WHO classification: An insight into the rarer morphological subtypes

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Introduction
Pituitary tumours may express somatostatin receptors (SSTR), which are a potential drug target to achieve tumour reduction and control of hormone secretion. There is a well-established role for somatostatin analogues in the management of acromegaly and Cushing's disease. The recent 2022 WHO classification of pituitary tumours provides a comprehensive approach to the diagnosis of pituitary tumours, allowing identification of additional morphological subtypes. Our aim is to assess SSTR expression in a large cohort of pituitary tumours and to determine patterns of expression in the rarer morphological subtypes identified under this new classification system.
Methodology
We conducted a retrospective study of pituitary tumours archived at the Institute of Clinical Pathology and Medical research at Westmead Hospital from 2011 to 2018. Immunohistochemistry was performed on each tumour to evaluate for expression of pituitary hormones, transcription factors (PIT1, TPIT, SF1), co-factors (GATA3, oestrogen receptor), somatostatin receptors (SSTR2A, SSTR5) and cytokeratin (CK 8/18). After reclassification according to the 2022 WHO classification of pituitary tumours, expression of SSTR 2 and 5 in each morphological subtype was assessed.
Preliminary Results
208 of 284 available pituitary tumours have been assessed and classified according to the 2022 WHO classification. SSTR2 expression was positive in 72.2% of PIT1 tumours, 43.9% gonadotroph (SF1) tumours and 33.3% corticotroph (TPIT) tumours. The corresponding expression of SSTR5 was 69.4% of PIT1 tumours, 1% gonadotroph (SF1) tumours and 18.2% corticotroph (TPIT) tumours. Among corticotroph tumours, expression of SSTR2 and SSTR5 was higher in Crooke cell tumours. In the PIT1 group, 100% of mature plurihormonal tumours and immature PIT1 lineage tumours expressed both SSTR2 and SSTR5. Densely granulated (DG) somatotroph tumours preferentially expressed SSTR2 (100%) over SSTR5 (33.3%), whereas their sparsely granulated (SG) counterpart showed high expression of both SSTR2 (87.5%) and SSTR5 (100%). SG lactotroph tumours showed no immunoreactivity for either form of SSTR; while 50% of DG lactotroph tumours expressed either SSTR2 or 5. We identified 5 plurihormonal tumours which co-expressed PIT1 and SF1 and all were positive for both SSTR.
Conclusion
This is the first study to systematically assess SSTR expression in all subtypes of the 2022 WHO classification. We have demonstrated that mature plurihormonal PIT1, immature PIT1, SG somatotroph and plurihormonal PIT1+SF1 highly express both types of SSTR. Our findings may be useful in predicting therapeutic response to somatostatin analogues in the future.

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P132

Comparative Efficacy and Safety of Osilodrostat Vs Metyrapone for the Treatment of Cushing's Syndrome – a Matching-Adjusted Indirect Treatment Comparison

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Objectives
Endogenous Cushing's Syndrome (CS) is a rare, chronic condition that results in high morbidity, caused by prolonged exposure to elevated levels of circulating free cortisol levels. Osilodrostat, a newly approved steroidogenesis inhibitor, has been shown to achieve fast and high rates of cortisol normalization, improving manifestations of hypercortisolism in patients with Cushing's Disease (CD), a form of CS. We evaluated relative complete response (CR) outcomes at Weeks 12 and 36, and two discontinuation outcomes at Week 24 for osilodrostat vs metyrapone for patients with CS.
Methods
The LINC-4 and PROMPT clinical trials investigated osilodrostat and metyrapone, respectively, in patients with CS. All LINC-4 patients and 90% of PROMPT patients had CD; remaining PROMPT patients had other endogenous CS aetiologies. Efficacy endpoints of CR (mean urinary free cortisol [mUFC] $\leq$ 1.0 x the upper limit of normal) at Weeks 12 and 36, and safety endpoints of all cause discontinuation and discontinuation due to lack of efficacy or any adverse event at Week 24 were analysed. Unanchored matching-adjusted indirect comparisons were performed using LINC-4 patient-level data and published summary data for PROMPT. Four baseline characteristics identified as potential prognostic factors were adjusted for: age, sex, time since diagnosis, and mUFC. Estimated weights were applied to logistic regression models providing relative effect estimates through weighted odds ratios (ORs). Scenario analyses investigated a trade-off between the effective sample size of the matched population and inclusion/exclusion of baseline mUFC as a matching variable, a plausible but unconfirmed prognostic factor. For CR endpoints, two methods of imputing missing response observations were investigated: non-response imputation and last observation carried forward (LOCF).
Results
Non-response imputation results suggested treatment with osilodrostat was associated with significantly increased odds of CR compared with metyrapone at Week 12 (OR: 3.43; 95% confidence interval [CI]: 1.10, 10.65) and Week 36 (OR: 7.57; 95% CI: 2.22, 25.77). This implies osilodrostat patients have 3.43 and 7.57 times greater odds of experiencing normalized cortisol levels at Weeks 12 and 36, respectively. No significant differences between treatments were found for the discontinuation endpoints. Scenario analyses investigating the exclusion of baseline mUFC as a matching variable and the LOCF imputation method for missing observations had consistent results.
Conclusions
Our analyses suggest osilodrostat significantly increases the odds of achieving CR at Weeks 12 and 36 compared with metyrapone, implying osilodrostat is a more efficacious treatment option than metyrapone for reducing cortisol levels in patients with CS.

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P133

Rare adverse event of treatment with somapacitan after switch from somatotropine

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Introduction
Somapacitan is 23.3-kDa human GH derivate linked to small noncovalent albumin binding moiety that facilitates reversible endogenous albumin binding to delay somapacitan elimination. The longer half-life and improved pharmacodynamics allow injections once per week. Some patients find a daily regimen with established treatment difficult, especially because treatment may be lifelong or at least for several years. Poor adherence with medication can lead to poorer clinical outcomes. In studies somapacitane was well tolerated and no safety issues were identified.
Case report
We report a case of 38 years old women with congenital panhypopituitarism with pituitary dysplasia, posterior pituitary ectopy and disconnected pituitary stalk. Diagnosis of hypopituitarism was established when she was 8 years old. In the past PROP1 and LHX3 mutations were excluded. Patient received treatment with hydrocortisone 20 mg QD in divided doses, levothyroxine 100 µg QD, somatotropine 0.4 mg sc. QD, norgestrel/estrogen. Because she was not adherent to somatotropine treatment we started treatment with somapacitan 4 mg sc. QW. At the start of treatment, she was educated from nurse educator about correct handling and application of medication. She followed the recommendation to administer somapacitan by subcutaneous injection to the abdomen or thigh with regular rotation of injection sites. Before switch from somatotropine to somapacitan IGF-1 was 72 µg/l (69.0 – 227.0 µg/l), IGF-1 SDS was -1.825. Three days post second injection IGF-1 was 140 µg/l, IGF-1 SDS was 0.143. Approximately 4 weeks after start of treatment, she reported reduced subcutaneous tissue on the site of application. On evaluation lipoatrophy of diameter of about 10 cm were present at two sides of lower abdomen and in left and right tight. The reduction of fat tissue was confirmed with DXA. Otherwise, she reported more energy, improved quality of life and treatment satisfaction. IGF-1 SDS was in target range. We discontinued treatment with somapacitan and re-started treatment with somatropine. On follow-up visit 1 month after discontinuation of somapacitan partial improvement in lipoatrophy was noted.
Discussion and conclusion
To our knowledge this is the first case of lipoatrophy in adult during treatment with somapacitan. Until today, lipoatrophy, which was reversable with change of application site, was described in 2 children in randomised control trial REAL 3.

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P134

Efficacy and Safety Analysis of Setmelanotide As a Novel Treatment for Hypothalamic Obesity

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Background
Hypothalamic injury and impaired melanocortin-4 receptor (MC4R) pathway signaling, often a result of surgery or radiation for a benign tumor, may lead to hypothalamic obesity (HO). After injury, sudden weight gain and appetite changes unresponsive to existing therapies develop. Setmelanotide, an MC4R agonist, is approved for chronic weight management in patients with certain MC4R pathway–associated diseases. We report interim results of a Phase 2 study of setmelanotide in HO (NCT04725240).
Methods
Patients aged 6-40 years with body mass index (BMI) $\geq$95th percentile (children 6 to $<$18 years) or $\geq$35 kg/m^2 (adults $\geq$18 years) and HO caused by structural hypothalamic damage secondary to craniopharyngioma or other benign brain tumor, surgical resection, and/or chemotherapy were enrolled. The setmelanotide dose was initiated by age, with 2-4 weeks of titration to 3.0 mg once daily, followed by 12-14 weeks at the target dose. The primary endpoint was the proportion of patients achieving $\geq$5% BMI reduction at Week 16. A key secondary endpoint was the composite proportion of children with $\geq$0.2-point reduction in BMI Z score and adults with $\geq$5% weight loss. Hunger was assessed daily using a numerical rating scale, where 0 = not hungry at all and 10 = hungriest possible.
Results
Eighteen patients were included (baseline mean [standard deviation (SD); range] age, 15.0 [5.3; 6-24] years and mean [SD] BMI, 38.0 [6.5] kg/m^2). A statistically significant proportion of patients achieved $\geq$5% reduction in BMI (88.9%; 90% confidence interval [CI], 69.0%-89.0%; $P<0.0001$); 72.2% experienced $\geq$10% reduction at Week 16. Mean (SD) change in BMI was $-$14.9% (9.6%; $n=17$). Mean (SD) percent change in hunger score was $-$45% (36.4%; $n=11$), a reduction of $-$2.9 (2.3) points from baseline. Frequent adverse events included nausea (61.1%), vomiting (33.3%), skin hyperpigmentation (33.3%), diarrhea (22.2%), and COVID-19 (22.2%). Two patients discontinued because of adverse events.
Conclusions
These early results warrant continued evaluation of setmelanotide in this population with a high unmet medical need and no approved therapies.

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Prolactinomas under high doses cabergoline in portuguese patients: The Resistant Prolactinoma Study

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Background
In 15% of prolactinomas there is dopamine agonist(DA) resistance. The clinical characteristics, the best diagnostic and therapeutic management of these cases have not been established so far.
Aim
To characterize patients taking a high dose cabergoline($\geq$ 3mg/week) and then describe clinical, biochemical and imaging features of cabergoline-resistant cases.
Methods
Retrospective study with 5 centers representing the contribution of Pituitary Study Group of SPEDM to "RESISTANT PROLACTINOMA STUDY"(ENEA Workshop and Study Committee). Clinical, biochemical and imaging data, diagnostic approaches, treatment options and outcomes were assessed. Cabergoline-resistant prolactinoma was defined as tumors treated with $\geq$3mg/week cabergoline for at least 6 months without achieving prolactin level normalization.
Results
Twenty patients, 55%($n=11$) males with a median age at diagnosis of 29 years(Interquartile range[IQR]:13) were included. Median initial prolactin level was 2117ng/ml(IQR:4005) and largest tumor dimension 28mm(IQR:25.3). All prolactinomas were macroadenomas. Parasselar, suprasselar and infrasellar intraesphenoidal growth was verified in 80%($n=16$), 80%($n=16$) and 60%($n=12$) respectively, and optic chiasm compression in 20%($n=4$). At diagnosis, 40%($n=8$) presented visual disturbances and 15%($n=3$) pituitary apoplexia. Hypogonadotropic hypogonadism was established in 85%($n=17$), central hypothyroidism in 30%($n=6$) and secondary adrenal insufficiency in 20%($n=4$). Cabergoline was the first treatment in 80%($n=16$). Eighteen prolactinomas(90%) were defined as cabergoline-resistant, and 75%($n=15$) did not decrease their size by $\geq$50%. Fifteen patients(75%) did an alternative treatment, achieving prolactin normalization in only 6,7%($n=1$) and decrease in $\geq$50% of tumor size in 33%($n=5$). Cabergoline median dose needed to decrease $\geq$50% of tumor was 4mg(IQR:0.5), the maximum median dose prescribed $>$3months without prolactin normalization was 3.25mg(IQR:1) and without tumor reduction was 3mg(IQR:0.5). One patient had metastasis and 30%($n=6$) had tumor relapse.

Conclusions
The male sex, tumor invasiveness and the magnitude of hyperprolactinemia are known predictors DA-resistance, and our results are consistent with that. The efficacy of alternative treatments in this type of lesions was scarce, either in prolactin normalization or tumor shrinkage. This study will contribute, we hope, to improve the understanding of the natural history of cabergoline-resistant prolactinomas.

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P136

Characteristics of follicular-stellate cells in newborn pituitary gland

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Introduction
The development of pituitary gland is orchestrated by genetic signals, transcription factors and signaling molecules with a crucial role in cell proliferation and differentiation. Anterior pituitary gland is formed by both granular (secretory) and agranular cells represented mainly by follicular-stellate cells. It is known that these cells form a supporting network around secretory cells and produce many kind of growth factors, but their major function remains unknown. Development of follicular-stellate cells and their implications in pathological processes of the adenohypophysis is scarcely covered in the literature.
Material and methods
54 newborn pituitary glands obtained from autopsy (ages between 0 days and 6 months) were evaluated using morphological (hematoxylin and eosin) and immunohistochemical staining (glial fibrillary acidic protein and S100 protein).
Results
The histopathological examination of the anterior pituitary gland revealed acidophilic-basophilic differentiation starting with 0 days. Pituitary anterior cells are distributed in nests and cords in first month after birth. The nests became dominant, starting one month, like in normal adult gland. Follicular-stellate cells, evaluated using GFAP and S100 protein, presented isolated IHC expression during first month, morphologically having oval and round shape. The follicular-stellate cells density increased progressively starting with five-seven days, with a more relevant IHC cytoplasmic reaction. The one-month specimens present follicular-stellate cells having star-like appearance with a strong IHC expression, being predominantly located in perivascular areas. Compared to S100 protein, GFAP analysis revealed more details about cell morphology (shape, orientation, tendency to form a network).
Conclusions
Few data regarding newborn pituitary gland morphological and immunohistochemical characteristics are found in the literature, even less about follicular-stellate cells. Their role is incompletely described, and it may be associated with normal and pathological development of pituitary gland. Newborn pituitary gland shows different microscopical aspect compared to adult. Follicular-stellate cells density increases with age, starting one week after birth.

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P137

The Effect of Dual-release vs Conventional Hydrocortisone on the Metabolic Profile in Secondary Adrenal Insufficiency

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Background and aim
The dual-release hydrocortisone Plenadren® has shown promising results of improved cardiovascular and metabolic profiles after treatment of adrenal insufficiency, possibly due to an improved circadian profile of cortisol, but results are ambiguous.
Aim
To further investigate the potential effect of dual-release hydrocortisone on the metabolic profile as compared to conventional hydrocortisone in patients with secondary adrenal insufficiency.
Material and methods
Design
An investigator-initiated 21 week open-label switch trial studying the effect of dual-release hydrocortisone vs conventional hydrocortisone on fatigue measured by ecological momentary assessments. In the present study, the metabolic outcome assessments at baseline on conventional stable hydrocortisone therapy and 16 weeks after switch to dual-release hydrocortisone were analysed.
Participants
Patients with adrenal insufficiency due to hypopituitarism and without diabetes (N = 27, 24 men/3 postmenopausal women). Outcomes: 24-h ambulatory blood pressure, body mass index (BMI), body composition assessed by Dual-Energy X-ray absorptiometry scan, blood samples for lipids, fasting glucose, and glycated haemoglobin, and markers of bone turnover (type 1 procollagen, collagen type 1 cross-linked C-telopeptide, osteocalcin, receptor activator kappa-B ligand, osteoprotegerin, and sclerostin).
Results
Median age[range] was 62 years[38–73]. The dose of conventional hydrocortisone and dual-release hydrocortisone did not differ significantly (median[range]: 20[10–35] mg and 25[10–35] mg, respectively, P= 0.1). Ten patients above the age of 50 years had osteopenia at baseline while none were diagnosed with osteoporosis. After 16 weeks of treatment with dual-release hydrocortisone, no change in mean BMI was observed (difference(sem): -0.2(0.2) kg/m^2, P = 0.2), whereas mean total fat mass was reduced (difference(sem): -1.4(0.4) kg, P = 0.003). Mean total lean mass increased, however, non-significantly (difference(sem): +0.6(0.5) kg, P = 0.3). Mean glycated haemoglobin was reduced (difference(sem): -1.1(0.4) mmol/mol, P = 0.02), but the mean of fasting glucose and lipids did not change. Mean osteocalcin significantly decreased (difference(sem): -7.0(3.1) µg/l, P = 0.03), but the levels of the remaining bone markers were unchanged. No difference was observed in 24-h ambulatory blood pressure.
Conclusions
We observed an improved metabolic profile with reduced total fat mass and glycated haemoglobin as well as a non-significant increase in total lean mass after 16 weeks of treatment with the dual-release hydrocortisone Plenadren® compared to stable conventional hydrocortisone replacement therapy that could be explained by the more physiological circadian profile of dual-release hydrocortisone. However, we also found a decrease in osteocalcin concentrations indicating an inhibition of bone formation which contradicts previous findings.

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P138

Post operative copeptin does not predict occurrence of the syndrome of inappropriate antidiuresis (SIAD) after pituitary transsphenoidal surgery

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Introduction
The incidence of the syndrome of inappropriate antidiuresis (SIAD) post pituitary surgery is estimated at 3-20% with the condition potentially leading to significant morbidity and prolonged admission. Copeptin, a surrogate marker for vasopressin activity, has been shown to be a diagnostic tool in the diagnosis of AVP deficiency (formerly known as diabetes insipidus) post pituitary surgery. There is limited data regarding the utility of copeptin in predicting SIAD post pituitary transsphenoidal surgery (TSS). The aim of this study was to evaluate the predictive value of copeptin for SIAD post TSS.
Methods
Retrospective analysis of copeptin measured at day 1, day 2 and day 8 post pituitary surgery where data available in consecutive patients undergoing TSS (November 2017 to October 2022). All patients were fluid restricted to 1.5L post TSS except for patients who developed AVP deficiency. Incidence of post TSS SIAD was noted from the electronic patient records and defined as Na < 135 mmol/l with serum osmolality < 275 mOsm/kg, urine osmolality > × 100 mOsm/kg, urine sodium > × 30 mmol/l, normal adrenocortical and thyroid function or replaced postoperatively, in euvolemic patients not on diuretics. Logistic regression and Receiver Operating Characteristic (ROC) curves were performed to investigate the value of copeptin in predicting SIAD.

Results
Post TSS copeptin was measured in 133 patients; mean age 34 years (SD = 17 years) ; 45% (60/133) female. Sixteen patients (12%) had SIAD within 8 days of surgery. Copeptin results were available in 123, 53 and 89 patients for day 1, day 2 and day 8 post TSS, respectively. Logistic regression for day 1 copeptin to predict SIAD gave odds ratio (OR) of 0.98 (95%CI 0.85-1.14, $P=0.82$) and an area under ROC curve (AUC) of 0.49; day 2 copeptin OR was 0.96 (95%CI 0.73-1.26, $P=0.76$) with AUC of 0.57; day 8 copeptin OR was 0.98 (95%CI 0.85-1.12, $P=0.73$) with AUC of 0.44. Logistic regression for day 1 sodium to predict SIAD revealed OR of 0.81 (95CI% 0.69-0.95, $P=0.01$) with AUC of 0.70, which remained unchanged after addition of day 1 copeptin to the day 1 sodium regression model.
Conclusions
Incidence of SIAD in our cohort is comparable to published data. We find that post operative copeptin is not helpful in predicting post TSS SIAD and hence would not recommend its use for this purpose.

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P139

Patients with acromegaly continue to derive clinical benefit from pasireotide long-acting release (LAR) for up to 12 years of treatment: Follow-up analysis of patients who received pasireotide during the clinical trial programme

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Introduction
Acromegaly is associated with significant morbidity and reduced quality of life. A robust clinical programme (14 trials) established pasireotide as an effective second-generation somatostatin receptor ligand for the treatment of various endocrine conditions, including acromegaly. Patients who completed a previous pasireotide trial and continued to receive clinical benefit, according to the parent study investigator, could continue treatment in the B2412 rollover study, which assessed long-term safety and clinical benefit.
Methods
This ongoing, open-label, multicentre, Phase IV study allows continued treatment for patients with acromegaly, Cushing's disease or other endocrine disorders who completed a pasireotide parent trial (NCT01794793). Here, we analysed patients with acromegaly who received pasireotide LAR in four parent studies (B2219, C2305, C2402, C2413) and ≥ 1 dose during the rollover, including cumulative data from parent study baseline to rollover interim data cut-off (1 November 2021). The B2412 study primary objective was to evaluate long-term safety, determined by adverse event (AE)/serious adverse event (SAE) frequency.
Results
Overall, 211 patients from 23 countries entered the rollover from four parent studies. At data cut-off, 59.2% of patients ($n=125$) were continuing treatment, 24.2% ($n=51$) had completed the study and 16.6% ($n=35$) had discontinued the study. The most common reason for study discontinuation was AEs ($n=12$; 5.7%). Median (min − max) exposure from first dose in the parent study to rollover data cut-off was 64.0 months (9–148), with a median (min − max) average dose of 44.8 mg/month (6–69). The most common AEs considered by the investigator to be treatment related from the first dose in the parent study to rollover data cut-off ($\geq 10\%$ of patients) were hyperglycaemia (34.1%), cholelithiasis (25.6%), diabetes mellitus (not further specified; 25.1%) and diarrhoea (16.6%). The most common AE leading to treatment discontinuation was hyperglycaemia (1.9%). AEs that most frequently required additional therapy ($\geq 20\%$ of patients) were hyperglycaemia (28.9%) and diabetes mellitus (not further specified; 26.5%). SAEs were reported by 29.4% of patients ($n=62$), most commonly cholelithiasis (6.2%) and COVID-19 (3.3%); all other SAEs were reported with $<1\%$ frequency. Altogether, $>94\%$ of patients were assessed as deriving clinical benefit from pasireotide LAR treatment at all study visits.
Conclusions
Pasireotide is well tolerated and provides clinical benefit for up to 12 years of treatment in patients with acromegaly. Hyperglycaemia, an AE often reported during the first 3 months of pasireotide treatment, is manageable, usually without the need for treatment discontinuation.

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P140

Molecular and clinical relevance of the somatostatin system in brain tumors

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High-grade astrocytomas (HGAs) remain the most prevalent and malignant brain tumor based on its locally aggressive behavior, being glioblastoma (grade-IV astrocytoma) the most lethal. The current standard treatment for glioblastomas consists of surgery followed by radiotherapy and/or chemotherapy. However, the average period of survival is about 14 months after the first intervention. Therefore, there is a clear clinical need for the identification of novel diagnostic, prognostic and therapeutic tools to manage and treat these brain pathologies. In this context, somatostatin analogues (SSAs) are efficacious and safe treatments for a variety of endocrine related tumors, but the presence of somatostatin receptors (SSTRs) and pharmacological effects of SSA on HGAs are poorly known. Specifically, we have recently reported that the truncated splicing variant of SSTR5, sst5TMD4, is overexpressed and associated with increased aggressiveness in glioblastomas. In this study, we demonstrated that the expression levels of the 5 canonical receptors (SSTR1-5) were significantly down-regulated in HGAs compared to non-tumor samples using different human cohorts (both internal and external cohorts). Notably, SSTRs expression levels were inversely correlated with the tumoral grade, and, consequently, with the aggressiveness of HGAs. Moreover, ROC curve and survival analysis demonstrated the potential value of SSTRs, mainly SSTR1 and SSTR2, as novel diagnostic and prognostic biomarkers. Additionally, lower expression levels of SSTRs were associated with aggressive parameters (i.e., IDH wildtype status, classical/mesenchymal subtypes, etc.) showing a potential pathophysiological role of the somatistatin-system in HGAs. Notably, treatment with different SSAs (octreotide, pasireotide) and specific receptor-agonists (SSTR1/SSTR2/SSTR5 agonists) significantly reduced cell proliferation in primary patient-derived glioblastoma cell cultures. Altogether, this study demonstrated that SSTRs expression is dysregulated in HGAs vs. control brain tissues and could represent a novel souse of diagnostic and prognostic biomarkers, since their expression is associated with critical clinical and pathological features. Moreover, our data unveil clear antitumoral effects of SSAs on HGAs, opening new avenues to explore their potential as targeting therapy for these devastating brain pathologies.

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P141

177Lu DOTATATE Peptide Receptor Radionuclide Therapy (PRRT) in advanced Phaeochromocytomas and paragangliomas (PPGL) – a single centre experience at a ENETS Centre of Excellence

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Introduction
Phaeochromocytomas and paragangliomas (PPGL) are rare neuroendocrine tumours with no standardised protocol for treatment. ^{177}Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) is an emerging treatment option for patients with metastatic and/or inoperable PPGL, and with low toxicity. We

present our experience with PRRT in advanced PPGL, treated in a ENETS *Centre of Excellence*.
Materials and Methods
165 patients with PPGL were screened retrospectively to identify cases with progressive disease and/or inoperable PPGL, treated with 2 or more cycles of ^{177}Lu-DOTATATE. Clinical (changes in antihypertensive medications or catecholaminergic features), radiological response rate (assessed by review of radiology reports and a formal RECIST assessment will be completed) and biochemical (plasma free metanephrines) responses were evaluated 8-12weeks after the last cycle of PRRT. Toxicity was assessed according to CTCAE v5.0. Progression Free Survival (PFS) was estimated using Kaplan Meier Survival analysis. Median Overall Survival (OS) was not reached.
Results
A total of 19 patients (4 phaeochromocytoma, 15 paraganglioma) were included (age range: 35-84 years, germline SDHx pathogenic variant found in 53%, elevated normetaphrines in 53% at baseline). Median duration of follow up was 30 months(range: 5-114) from the date of cycle 1 of PRRT. Patients received PRRT due to radiological progression 15(79%) or inoperable disease with metastases at baseline 4(21%) (median cycles: 4; median cumulative dose: 24.5 GBq). Radiological response was evaluable in 17 patients with PPGL, which confirmed stable disease in 11 patients (65%), and progressive disease in 6 patients (35%). Of the total cohort, median PFS from the date of the first cycle of PRRT was 32 months (95% CI, 4.61-59.39). Median PFS for the paraganglioma subgroup and inoperable disease at baseline was 30 months (95% CI, 3.67-56.33), 12 months (95% CI, 9.45-14.55) respectively. Median PFS for the patients with progressive disease at baseline, phaeochromocytoma subgroup and OS could not be assessed due to the relatively small patient numbers. Of patients with elevated metanephrines at baseline (10, 53%), anti-hypertensive doses were unchanged in 6 (60%), increased in 2 (20%), and increased transiently in 1 (10%). No CTCAE grade 3/4 cytopenia or nephrotoxicity was seen. One patient received 2 cycles of half standard dose PRRT due to baseline thrombocytopenia but therapy was then suspended due to progressive disease.
Conclusion
PRRT is an effective treatment option for patients with metastatic PPGL with encouraging PFS and low toxicity. It is a feasible alternative to chemotherapy and ^{131}I-MIBG but prospective and comparative studies are needed.

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P142

Characterization of a large cohort of patients with "micromegaly": long-term follow-up and preliminary data on treatment response

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Background
In a previous study, we retrospectively analysed a group of patients with high insulin growth factor 1 (IGF1) but normal growth hormone (GH) suppression, identifying among them a subgroup of "micromegalic" patients presenting with clinical features of acromegaly and high rate of comorbidities. We therefore expanded our cohort of patients, extended the follow-up time and collected preliminary data on treatment response aiming to better characterize this condition.
Patients and methods
We enrolled 86 patients (53 included in our previous study, mean age 48 ± 17 years, 56 females and 30 males) referred to our Endocrinology Unit between 2008 and 2022, presenting with persistently high IGF1 and adequate GH nadir after glucose load (<0.4 ng/ml according to most recent guidelines). We divided them in two groups: with (G1, "micromegaly", $n=28/86$) or without (G2, 58/86) clinical features of acromegaly. We performed systematic clinical-instrumental screening of acromegaly-related comorbidities (arterial blood pressure and glucose metabolism evaluation, thyroid ultrasound for goitre, colonoscopy and/or faecal occult blood for colonic polyposis, echocardiography for cardiopathy, polysomnography and ESS questionnaire for OSAS). We recorded biochemical and clinical data from diagnosis to the last available follow-up. Finally, we collected preliminary data of a small subgroup of patients who underwent medical or surgical treatment.
Results
In G1 group ("micromegaly") we confirmed a higher prevalence of comorbidities vs G2 (median comorbidities for each patient 4 vs 3, $P=0.001$), especially goitre ($P=0.009$), carpal tunnel ($P=0.003$) and malignant neoplasms ($P=0.03$). During a mean follow-up time of 6 ± 3 years, IGF1 and GH nadir levels did not significantly change, whilst we observed an increase in random GH values in G1 vs G2 patients ($P=0.03$). Four patients with highly suggestive clinical features of acromegaly and typical comorbidities were selected for treatment: two were treated with somatostatin analogues and two underwent transsphenoidal surgery (1 micro and 1 macroadenoma, both histologically proven GH+). All treated patients showed normalization of IGF1 values and referred subjective improvement in clinical symptoms.
Conclusions
Our preliminary data suggest that "micromegalic" patients present typical comorbidities of acromegaly and can benefit from either medical or surgical therapy.

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P143

Role of fT4 and TSH-index fluctuations as early diagnostic tools in milder forms of central hypothyroidism: data from 221 patients with pituitary lesions from a single tertiary center

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Diagnosis of Central Hypothyroidism (CeH) is commonly given when FT4 concentrations are below the lower limit of normal range. A reduction in FT4 concentrations greater than 20% was proposed in ETA 2018 Guidelines as an unphysiological fluctuation indicating the onset of milder forms of CeH with FT4 still within the normal range. Similarly, TSH-index was proposed to quantify thyrotrope reserve, hence as a tool to detect patients at risk of CeH. Here we verified the performance of these parameters for the diagnosis of CeH in 221 patients with pituitary lesions – 127 adenomas and 94 empty sellas – and at least three evaluations of Thyroid Function Tests (TFTs, i.e. paired detection of TSH and FT4) during a median follow-up of 4 years. We also studied TFTs of 42 matched controls, selected from a cohort of euthyroid patients (TSH 0.5-4.5 mU/l) with multinodular goiter and negative thyroid autoimmunity followed up during the same period. We evaluated FT4 concentrations, TSH, TSH-index and defined two derived parameters, FT4var and ΔTSH-index, which were respectively the greatest reduction of FT4 and TSH-index compared to their median value for each patient (FT4var=FT4 nadir – median FT4; ΔTSH-index = TSH-index nadir – median TSH-index). The diagnosis of CeH+ was made according to ETA 2018 Guidelines. In CeH- patients, FT4var did not differ statistically in patients with adenomas, empty sellas and controls (varying from 15 to 25%; P=n.s.). Consistently, in patients diagnosed with CeH+, FT4var (and its percentage value FT4var%) was able to distinguish patients harbouring adenomas or empty sellas with and without CeH [CeH+ vs CeH-: FT4var -3.1 ± 1.9 vs -1.4 pmol/l (IQR-2.1; -0.7), $P=0.03$; FT4var% -28% ± 15 vs -8% (IQR -14; -5), $P<0.001$]. Moreover, in our cohort, TSH-index allowed in distinguishing patients harbouring a pituitary lesion CeH+ vs CeH-, at baseline [CeH+ vs CeH– 1.8 (IQR 0.8; 2.2) vs 2.5 (IQR 2; 2.9); $P<0.001$]) and during follow-up [CeH+ vs CeH–: 1.3 ± 1.3 vs 2.5 ± 0.7, $P<0.001$]. In conclusion, both patients with pituitary lesions and controls show fluctuations of TFTs around an individual set-point. In patients with pituitary lesions such as adenomas and empty sellas, FT4var, FT4var% and TSH-index are useful tools able to highlight milder forms of CeH. We found that a fluctuation of FT4 value (FT4var) or FT4var% respectively greater than 3.1 pmol/l or 28% indicated the onset of mild CeH. The coexistence of a TSH-index lower than 1.3 may be useful to support this challenging diagnosis.

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P144

Glucocorticoid Resistance Syndrome: a Rare Disorder that we Must not Forget. A Clinical Case

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Primary generalized glucocorticoid resistance or Chrousos syndrome is a rare disorder, which affects all tissues expressing the human glucocorticoid receptor. It has been defined by an absence of overt Cushing's syndrome (CS) signs (no skin weakness, muscle atrophy, or osteoporosis) associated with biological

hypercortisolism consisting of high urinary free cortisol (UFC) and an absence of negative feedback loop of cortisol on HPA, defined as 8-AM cortisol level >50 nmol/l after overnight 1 mg DXM suppression test. It is characterized by tissue insensitivity to glucocorticoids caused by genetic defects in the NR3C1 gene. To date, 31 NR3C1 loss-of-function mutations have been reported

Case Report

A 31-year-old woman was referred to our hospital to continue monitoring and treatment of ACTH-dependent CS. When she was 26-year-old an analysis was performed for a hormonal study prior to laser treatment for hirsutism, where elevated cortisol was evidenced, being referred to an outpatient clinic of endocrinology. An increased UFC was found of 2 times over the upper limit of normal (234 and 248 mg/dl), a disturbed 1-mg and 2-mg dexamethasone suppression test with a cortisol value of 8,14 and 14 µg/dl respectively and a high normal ACTH level of 136 pg/ml where evidenced. Pituitary imaging with magnetic resonance imaging (MRI) showed no pituitary adenoma. A bilateral petrosal sinus sampling was performed showing a lack of ACTH gradient. A whole-body CT was performed to evaluate tumors suggestive of ectopic ACTH secretion with no findings. In 2021 she arrived at our hospital. At physical examination her blood pressure was 110/70mmHg, her body mass index was 23.5 kg/m2. She hadn't plethoric facial appearance, no central obesity, no muscle atrophy, no ecchymoses and no hirsutism. She had regular menses. No osteoporosis. Levels of UFC (243 mg/dl), ACTH (147pg/ml), DHEAS (675 mg/dl), androstenedione (6.9ng/ml), testosterone (0.59ng/ml) and 17OHprogesterone (3.90ng/ml) where similar than five years ago. Aldosterone concentration and ratio aldosterone/DRC were normal. A CT scan shows bilateral adrenal hyperplasia. With a suspected diagnosis of glucocorticoid resistance syndrome, we proposed a NR3C1 sequencing study in which no pathogenic variants were identified

Conclusion

In patients with biological hypercortisolism without signs and symptoms of CS we must think in a GC resistance syndrome. There had been several cases reports of patients with clinical and/or biochemical glucocorticoid resistance without alterations in glucocorticoid receptor gene NR3C1

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P145

Somatostatin receptor type 2 (SSTR2) expression regulation by miR-375 in a murine pituitary corticotroph tumor cell model

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Cushing's disease (CD), caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary tumor, is the most common form of hypercortisolism. Pituitary surgery is the first-line treatment of CD and medical treatment is an alternative second-line approach to control cortisol excess. Long-term exposure to glucocorticoids (GC) downregulates the expression of somatostatin receptor type 2 (SSTR2) but not type 5 (SSTR5) in human and mouse ACTH-secreting tumor cell cultures; thus octreotide, the somatostatin receptor ligand (SRL) with high affinity for SSTR2, failed to show any significant decrease neither in circulating ACTH and, consequently, cortisol levels, nor on tumor growth in CD patients. A recent study showed that in vitro dexamethasone treatment of a murine corticotroph tumor cell model induces an increase in miR-375 expression. The sequence analysis of SSTR2 revealed a binding site for miR-375. This finding supports the hypothesis that GC excess might downregulate SSTR2 expression through an epigenetic mechanism. The aim of the current study was to evaluate whether miR-375 is involved in the regulation of SSTR2 expression in a murine corticotroph tumor cell model AtT20. SSTR2 gene and miR-375 expression levels were evaluated by RT-qPCR in murine corticotroph (AtT20) and compared with somatotroph (GH3) cell lines. To evaluate the involvement of miR-375 in the regulation of SSTR2 protein expression, 24h miR-375 knocking-down was performed in AtT20 and SSTR2 protein levels were evaluated by western blot (WB) and immunofluorescence (IF). Moreover, miR-375 expression levels were also evaluated in 6 human corticotroph pituitary tumors and 2 normal pituitaries, whereas miR-375 circulating levels were evaluated in 21 CD patients and 19 healthy subjects by RT-qPCR. The results demonstrated an inverse SSTR2 and miR-375 expression in AtT20 and GH3 cells, with low levels of SSTR2 messengers and high levels of miR-375 in AtT20 and an opposite expression pattern in GH3 cells. After 24h of miR-375 knocking-down, induced by miR-375 inhibitor, SSTR2 protein expression, evaluated by WB and IF, was significantly increased in AtT20 ($P=0,0310$ and $P=0,0154$, respectively), compared to the control. Furthermore, miR-375 showed a higher expression in human corticotroph pituitary tumors than in normal pituitaries, as well as a higher and significant miR-375 circulating levels were observed in CD patients ($P<0.0001$) compared to healthy subjects. In conclusion, these data suggested that SSTR2 protein expression might be epigenetically downregulated by miR-375 in corticotroph pituitary tumors. Functional assays are mandatory to evaluate the role of SSTR2 in the condition of miR-375 knock-down.

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P146

Dopamine agonist-resistance in patients with macroprolactinoma: prevalence and predictive factors

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Introduction

Dopamine agonists, mainly cabergoline and bromocriptine, represent the first-line treatment option in the management of prolactinomas. They allow prolactin normalization and tumor shrinkage. However, a subset of individuals with macroprolactinoma could exhibit a varying degree of resistance to dopamine agonists. The aim of this study was to determine the prevalence of dopamine agonist-resistance in patients with macroprolactinoma and to assess its predictive factors.

Methods

This was a single-center, retrospective study including 52 patients with macroprolactinoma. All enrolled patients were treated with dopamine agonists (cabergoline or bromocriptine). Resistance to dopamine agonists was defined as failure to achieve normoprolactinemia and/or 30% tumor shrinkage. Age, gender, epidemiological parameters, medical history, and clinical and paraclinical data were collected from medical records.

Results

Twenty-seven men and 25 women were enrolled in this study. Their mean age at the diagnosis of macroprolactinoma was 34.7 ± 14.9 years. The median baseline prolactin level was 1879 µg/l. The mean baseline macroprolactinoma size was 35 ± 17 mm (extremes: 11-77 mm). Macroprolactinoma was invasive in 73% of cases, with hemorrhagic or necrotic components in 52% of cases. Dopamine agonist resistance was observed in 16 patients (31%). Univariate analysis showed that age at diagnosis <30 years (OR=5, 95%-confidence interval (95%-CI):1.13-14.29, $P=0.011$), baseline prolactin level > 7000 µg/l (O $r=4.86$, 95%-CI:1.14-20.63, $P=0.035$), invasive adenoma (OR=10.26, 95%-CI: 1.20-87.55, $P=0.018$), presence of hemorrhagic or necrotic components (OR=28.5, 95%-CI: 3.27-248.17, $P=10^{-3}$), and tumor size > 40 mm (OR=7, 95%-CI: 1.71-28.54, $P=0.004$) were associated with dopamine agonist-resistance. In multivariate analysis, the presence of hemorrhagic or necrotic components was the only independent predictor of dopamine agonist-resistance (adjusted-O $r=28.68$, $P=0.005$).

Conclusion

Dopamine agonist-resistance was frequent in patients with macroprolactinoma. Its predictive factors included young age, invasive tumor, high baseline prolactin levels, tumor size, and the presence of hemorrhagic or necrotic components. The latter was the only independent predictor of treatment resistance.

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P147

Baseline clinical and treatment characteristics of dopamine agonist treated patients in a Dutch national cohort of patients with prolactinoma

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Introduction

Dopamine agonists (DA) are first-line treatment for prolactinomas and effectively control hyperprolactinemia in most patients. However, side effects may negatively impact health-related quality of life; and post-withdrawal remission rates are low, resulting in prolonged DA treatment.

Methods

Dutch multicenter prospective observational cohort study mapping standard care for 316 prolactinoma patients. Baseline clinical characteristics and treatment outcomes of 210 DA treated (DAT) patients are described (mean age 49.4±15.4 years; females $n=122$, 58.1%). 106 patients were not treated with DA at inclusion.

Results
Current prolactin levels -available for 155 patients- were elevated above the sex specific upper limit of normal in 54 (34.8%) patients, not different between males and females. Imaging data -available for 60 patients- showed 21 (35.0%) microprolactinomas, 23 (38.3%) macroprolactinomas, 1 (1.7%) giant prolactinoma, whereas in 10 (16.7%) patients no adenoma was visible, and 5 (8.3%) had a postoperative remnant. Males had more macroprolactinomas (15 (62.5%) vs 8 (22.2%), $P<0.001$). Galactorrhea was reported by 15/119 (12.6%) patients (males $n=1/50$ (2.0%) vs females $n=14/69$ (20.3%), $P=0.004$). Hypogonadism was reported by 42/153 (27.5%) patients, and subfertility by 10/118 (8.5%) patients, not different between males and females. DA side effects -measured using the PROCTCAE questionnaire ($n=155$)- were gastro-intestinal tract symptoms (e.g. diarrhea, constipation, nausea) in 63 (40.6%) patients (males $n=14/68$ (20.6%) vs females $n=49/87$ (56.3%) $P<0.001$). 77 (50.0%) patients reported fatigue (males $n=22/68$ (32.4%) vs females $n=55/86$ (64.0%) $P<0.001$). 41 (26.6%) patients reported concentration loss (not different between males and females).
Conclusions
In this Dutch national cohort of patients with prolactinoma, 210 DA treated patients were identified. We describe baseline clinical characteristics and significant sex differences for most outcomes of interest, which need to be taken in to account when interpreting treatment outcomes of prolactinoma patients.

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P148

Uncontrolled Acromegaly, Diabetes Mellitus and Metabolic Syndrome are the Main Risk Factors of Colon Polyposis Recurrence in Patients with Acromegaly

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Colon polyps represent a frequent complication of acromegaly. Knowledge about prevalence and risk factors of polyps' recurrence in acromegalic patients is still limited. The current retrospective study aimed at investigating polyps' prevalence and recurrence risk factors in acromegalic patients. One hundred and forty-three patients (73 males, 70 females) referring to "Federico II" university diagnosed with acromegaly from 2000 to 2022 who underwent at least one colonoscopy have been considered in the present study. Hormonal, metabolic parameters and colonoscopy result were evaluated. Colonoscopy was performed at diagnosis in 104 (72.7%) and after a disease duration of 9.6 ± 5.5 years in 39 patients (27.3%). Polyps were found in 39.4% and 38.5 %, respectively ($P=0.91$). At diagnosis, polyps were found more frequently in older ($P=0.09$), diabetic ($P=0.007$) patients, with higher number of systemic complications ($P=0.004$). Prevalence of polyps at diagnosis was significantly higher in patients with presumed disease onset greater than 5 years (median, $P=0.013$). Patients with IGF-I ($P=0.003$) and fasting glucose (FG, $P=0.01$) above the median showed significantly higher prevalence of polyps than those below. In patients who underwent colonoscopy after the diagnosis, age at diagnosis of acromegaly ($P=0.03$), FG ($P<0.001$), HbA1c ($P=0.001$), HOMAIR ($P=0.05$), and number of systemic complications ($P=0.02$) were significantly higher in patients with polyps than those with a normal colonoscopy. Overall among diabetic patients, polyps prevalence was significantly higher in patients administered with insulin than in those treated with oral antidiabetic drugs (35% vs 6.25%, $P=0.04$). Forty-nine patients (34.2%) underwent multiple evaluations with 10-years median of colonoscopy follow-up. Among patients with polyps at first colonoscopy, recurrence was present in 41.6% at the second evaluation, particularly in patients with uncontrolled acromegaly ($P=0.06$), glucose metabolism alterations ($P=0.002$), metabolic syndrome (MS, $P=0.04$), and diabetes treated with insulin therapy ($P=0.02$). In patients treated with SRLs polyps recurrence was lower than those treated differently (29.4% vs 66.6%, $P=0.07$). 30.4% of patients with first negative colonoscopy had polyps at the second evaluation, particularly those with uncontrolled acromegaly ($P=0.03$), smoking habit ($P=0.002$) and MS ($P=0.06$). Overall, five patients (3.5%) had colon cancer, diagnosed in two cases at acromegaly diagnosis and in three during the follow-up, after a mean disease duration of 18 years. Colonic polyposis is a major concern in patients with acromegaly. Regular colonoscopy is mandatory in this population. Recurrence is more common in patients with uncontrolled acromegaly, glucose metabolism alterations, and MS, requiring frequent colonoscopy evaluations.

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P149

Is a 20% decrease in free T4 (fT4) levels a reliable marker of secondary hypothyroidism in patients with non-functioning pituitary macroadenoma (NFPA)?

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Background
Central hypothyroidism can be difficult to diagnose as TSH values often reside within the normal range. The Endocrine Society clinical guideline for hormone replacement in hypopituitarism suggests levothyroxine is indicated for treatment of secondary hypothyroidism where fT4 levels decrease by $\geq$20%. To determine the reliability of this biochemical marker of secondary hypothyroidism we evaluated evolution of TFTs over time within a cohort of NFPA.
Methods
A retrospective review of TFTs was undertaken during 2000 to mid-2019 whilst using the Siemen's Centaur assay to measure fT4 levels. Patients with NFPA were identified from the departmental database. Patients with a history of CNS/pituitary irradiation; more than one pituitary surgery; on levothyroxine or identified with primary or secondary hypothyroidism at their first assessment during the study period, were excluded from analysis. Demographic, adenoma characteristics, treatment and hormone data were collected from primary and secondary care records.
Results
A total of 67 patients were identified, 39 male and 28 female with a mean age 58.0 (range 29.0-89.7) years. 34 patients underwent surgery and 33 patients did not. Mean follow-up was 5.2 (range 0.25-15.1) years. The indication for surgery in the majority of patients was visual compromise from optic chiasm compression. A total of 22/67(32.8%) patients experienced a drop of $\geq$20% in their fT4 levels from baseline (either first thyroid function test at diagnosis or first post-operative result in those who underwent surgery). Of the 22 patients, 12 showed subsequent recovery in their fT4 levels, whereas 10 did not recover during follow-up. In those who showed recovery 7, 2 and 3 had no, one or two hormone deficits. Similarly in those who did not recover 6, 2 and 2 had no, two or three additional hormone axis deficits. 12/67 patients saw a drop in their fT4 to below the reference range (10-20pmol/l), of whom 7 also showed a $\geq$20% decrease in fT4 values. 5 showed recovery of their fT4 levels and 7 a temporary decrease.
Conclusions
Variations of $\geq$20% in fT4 values occur in around a third of operated and non-operated NFPA on long-term follow-up. Around 50% of these episodes resolve spontaneously. Current guidelines may therefore lead to over diagnosis of secondary hypothyroid in patients with pituitary adenoma. Surveillance of repeated fT4 levels and symptoms is indicated before a diagnosis of secondary hypothyroidism can be established.

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P150

Epidemiology, clinical presentation, treatment and outcome of acromegaly in the island of Crete, Greece. 27 years of follow up study

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Background
Acromegaly is a rare endocrine disorder due to growth hormone excess attributed to a pituitary tumor, in most cases. Epidemiological data of acromegaly are derived from national tumor registries or population studies while there are no published data in the Greek population except for a few small studies regarding treatment outcome.
Methods
We carried out a retrospective ongoing observational study to determine the epidemiology, presentation and outcome in patients with acromegaly in University Hospital of Heraklion, Crete, Greece, referal center for acromegaly, from years 1995 to 2022. Age at diagnosis, estimated delay in diagnosis, clinical, biochemical and imaging data at presentation and post treatment were recorded.
Results
Forty-two patients were included in the analysis (28 females, 14 males). The mean age at diagnosis was 45.5 $\pm$17 years and the mean follow-up time was 12,5$\pm$ 14 years. Nine patients (21.4%) presented before the age of 30 years. The time lag from the onset of symptoms to diagnosis was 5,2 years. The three most common clinical features at diagnosis were acral changes (88%), coarse facial features (75%), headache(47,5%,). Nine patients (21.4%) had a microadenoma while 24 (57.1.%) harbored a pituitary macroadenoma. No size data were

available for 21.5% patients. In our series, 10 patients (23.8%) had a family history of pituitary adenoma including a family with Familial Isolated pituitary adenoma (FIPA) due to *AIP* mutation. Musculoskeletal manifestations were present in 46.4%, diabetes mellitus in 26.8% and hypertension in 16%. Fifteen patients (36.5%) declined surgery and were given medical treatment (somatostatin analogues in 31,7%, dopamine agonist in 2.4%, and combination therapy in 2,4%). Twenty seven patients (63,5%) underwent transsphenoidal surgery (TSS); two of them (5.4%) had a second surgery, Six patients (14.6%) received radiotherapy. Histology was available for 11 patients; densely granulated tumors were 1,7 times more frequent than sparsely granulated (26.3 vs 15.7%), whereas 10,4% were mixed mamosomatotrophs. There was one case of mixed gangliocytoma/sparsely-granulated somatotrophinoma. Disease remission was obtained in 14 patients (34%) and almost 50% had stable disease. The mean time interval from start of treatment till achievement of biochemical control was approximately 2 years. Seven patients (16%) remained biochemicaly uncontroled.

Conclusions

This is the first epidemiological study for acromegaly in Greece. Our results are similar to those of other international reports. We also confirm the data, of international registries that almost a third of all patients remain undertreated which underlies the importance for a better management.

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P151

Novel provocation test with MDMA (“ecstasy’) reveals oxytocin deficiency as a new pituitary entity in patients with central diabetes insipidus – a randomized placebo-controlled trial

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Introduction

Patients with arginine vasopressin deficiency (AVP-D), known as central diabetes insipidus (cDI), often report psychological symptoms such as heightened anxiety levels, difficulties describing emotions, and depressed mood despite adequate treatment with desmopressin. Given the anatomical proximity, disruptions of the hypothalamic-pituitary axis causing an AVP-D could also disturb the oxytocin (OXT) system. OXT regulates socio-emotional functioning, including fear reduction, attachment, emotion recognition, and empathy. Therefore, these psychological symptoms may be caused by an additional OXT deficiency. However, OXT deficiency has not been established as a pituitary entity, as no provocation test for OXT is currently available. Here, we aimed to investigate the OXT system stimulator 3,4-Methylenedioxymethamphetamine (MDMA, “ecstasy’) as a novel biochemical and psychoactive provocation test to reveal an OXT deficiency in patients with cDI.

Methods

Randomized, placebo-controlled, double-blind, cross-over study in 15 patients with cDI and 15 matched healthy controls. Participants underwent a psychological baseline evaluation, including the assessment of anxiety levels using the State-Trait Anxiety Inventory (STAI), mood using the Beck’s Depression Inventory (BDI), and alexithymia using the Toronto Alexithymia Scale (TAS). Participants were randomized to receive either a single oral dose of MDMA (100 mg) or placebo first. OXT samples were collected at 0, 90, 120, 150, 180, and 300 minutes after drug intake. Subjective effects in response to MDMA were assessed throughout the experiment. The primary outcome was the area under the plasma OXT concentration curve (AUC) after MDMA intake.

Results

Already at baseline, patients compared with healthy controls, showed significantly higher scores in anxiety (STAI: 41 points [IQR 34-48] vs. 28 points [24-31]; $P=0.02$), alexithymia (TAS: 47 points [38-59] vs. 30 points [29-37; $P=0.04$), and depression symptoms (BDI: 6 points [3-17] vs. 1 point [0-2]; $P=0.04$). In response to MDMA stimulation, in patients, there was only a minimal OXT change with 66 pg/ml [16-94], while in healthy controls, OXT increased by 658 pg/ml [355-914]. The AUC was 15.8 times (1485%), i.e., 85,678 pg/ml (95%-CI [-10,800 to -63,356], $P<0.001$), lower in patients compared with healthy controls. This lack of OXT in patients was associated with lower subjective effects such as “good drug effect,’ “feeling high,’ “satisfaction,’ “happy,’ “trust,’ “talkative,’ “openness,’ and “fear reduction’ compared with healthy controls.

Conclusion

These results lay the groundwork for OXT deficiency as a hypothalamic-pituitary entity. In patients with cDI, this lack in OXT was associated with reduced pro-social, empathic, and anxiolytic effects.

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P152

Protein tyrosine phosphatase receptors N and N2 regulate gonadotropin-releasing hormone neuron function

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Simultaneous knockout of the neuroendocrine marker genes *Ptprn* and *Ptprn2*, which encode the protein tyrosine phosphatase receptors N and N2, respectively, causes infertility of female mice while males are fertile. To clarify the mechanism of sex-specific roles of *Ptprn* and *Ptprn2* in mice reproduction, we analyzed the effects of their double knockout (DKO) on the hypothalamic-pituitary-gonadal axis. In DKO females, a delay in puberty and lack of ovulation were observed, supplemented by changes in ovarian gene expression and steroidogenesis. In DKO males, the testicular gene expression, steroidogenesis, and development of reproductive organs were not affected. However, in both sexes, pituitary luteinizing hormone (LH) beta gene expression and LH levels were reduced, while the calcium-mobilizing and LH secretory actions of gonadotropin-releasing hormone (GnRH) receptors were preserved. The expression of hypothalamic *Gnrh1* and *Kiss1* genes were also reduced in DKO females and males. The density of immunoreactive GnRH fibers was decreased in the median eminence in DKO females and males. The density of immunoreactive kisspeptin fibers was also decreased in the rostral periventricular region of the third ventricle of females and in the arcuate nucleus of females and males. Therefore, infertility in DKO females cannot be explained only by sex-specific gonadotroph impairment. Instead, changes in hypothalamic gene expression, specifically *Kiss1* in the rostral periventricular region of the third ventricle, might provide an alternative hypothesis due to its sexual dimorphism and involvement in puberty onset and ovulation.

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P153

Comparison of Clinical, Hormonal, Pathological and Treatment Outcomes of Ectopic ACTH Syndrome by Gender: Results of a Multicenter Study

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Objective

Data on gender comparisons of diagnosis, management and prognostic factors in Cushing’s disease are very limited, however, there is no such a comparison in

ectopic ACTH syndrome (EAS) in the literature. The aim of this study is to compare clinical and hormonal data, neuroendocrine tumor (NET) localization, treatment and survival outcomes in Cushing's syndrome due to EAS by gender.
Material-Methods
Eleven experienced centers from our country participated in this retrospective study. Clinical and hormonal features, tumor imaging, pathological results, treatment modalities and disease courses of the patients were evaluated.
Results
Fifty-four EAS patients (28 female and 26 male) were reviewed. The mean age at diagnosis is similar as 43 ± 18 years for females and 41 ± 14 years for males. Results of clinical characteristics and hormonal evaluations (ACTH, basal cortisol and 24-h UFC levels and results of dexamethasone suppression test) did not differ in both gender. However, insulin-requiring diabetes mellitus ($P=0.04$) and osteoporosis with fractures were more common in males ($P=0.03$). While number of patients with increased DHEA-S levels than upper limit of normal was found to be significantly higher in females ($P=0.002$), suppressed freeT4 and TSH levels consistent with central hypothyroidism were higher in males ($P=0.02$). At the diagnosis, 36 NETs (68% of females and 69% of males) were localized. Small cell lung carcinoma was higher in females than in males ($P=0.02$), the frequency of other NETs (typical/atypical bronchial carcinoid, thymic carcinoid/thymic neuroendocrine carcinoma-NEC, medullary thyroid carcinoma, pancreatic G1-G2 NET/pancreatic NEC and pheochoromocytoma) was not different. Curative surgery was performed on 61% of females and 46% of males. Tumor size, ki-67 labelling index and presence of local lymph node metastasis in pathological examination and distant metastasis rates were similar in both gender. In the follow-up, tumor became visible in 7 of 10 females and 4 of 8 males after medical treatment and/or bilateral adrenalectomy. Tumor could not be detected in 7 patients (3 females, 4 males) during a mean follow-up of 58 months. The overall remission rates (65% of females, 62% of males) and NET-related death rates (14% of females, 30% of males) at the last visit were similar.
Conclusions
While EAS has a similar disease course in many aspects in males and females, hyperglycemia and osteoporosis are more severe in males. Their severity may be due to the reduced beneficial effects of adrenal androgens on bone due to low DHEA-S level and the difficulty of glycemic control by central hypothyroidism.

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P154

Clinical utility of the Octreotide Challenge Test in Acromegaly

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Background
Acromegaly is a rare condition characterised primarily by tumourous production of excess Growth Hormone (GH) from a pituitary adenoma. The Octreotide Challenge Test (OCT) has been used in the RVI to predict short term efficacy of long-acting Somatostatin Analogue (SSA) therapy.
Aims
We retrospectively reviewed the OCT results of all patients with acromegaly treated at RVI from 2005 to 2021 to evaluate its clinical utility.
Methods
OCT protocol: blood sampling for GH is undertaken at baseline and then hourly for 6 h after SC administration of 100 mg of short-acting Octreotide. Data extracted: patient demographics, baseline GH and nadir GH on OCT, IGF1 level at presentation and after long-acting SSA therapy, follow-up MRI findings after SSA therapy.
Results
46/79 patients diagnosed with acromegaly had OCT. Female to male ratio was 3:2, with a mean age of 49 years and mean IGF1 of 3xULN at diagnosis. All patients demonstrated a reduction in GH on OCT, with a mean reduction of 72%. 25 patients received SSA pre-surgery or as long-term medical therapy. There was no relationship between reduction of GH on OCT and IGF1 suppression on SSA. Females were more likely to experience $>50\%$ reduction in IGF1 on SSA compared to males (78% vs. 56%, $P=0.04$). 18 patients underwent repeat imaging >6 months after SSA initiation and/or before surgery. Tumour shrinkage were demonstrated in 67% of cases. Shrinkage was most likely to be observed in females (66% vs. 33%, $P<0.05$). Average GH reduction on OCT was 68% in patients who demonstrated tumour shrinkage compared to 83% in those who did not ($P<0.05$).
Conclusions
OCT does not predict biochemical response to SSA therapy in our cohort. Female patients are more likely to have a better reduction in IGF1 and tumour shrinkage on SSA therapy compared to males. Tumour shrinkage is inversely related to GH reduction on OCT in our cohort.

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P155

Development of a new score to predict dopamine agonist resistance in patients with macroprolactinoma

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Introduction
Surgical treatment is indicated in patients with dopamine agonist-resistant macroprolactinoma. However, the resection of the tumor is usually partial because of fibrotic changes under long-term dopamine agonist therapy. Thus, early identification and management of patients at high risk of dopamine agonist resistance is crucial to a complete resection outcome and a better remission. The aim of this study was to develop a score predicting dopamine agonist resistance in patients with macroprolactinoma.
Methods
This was a single-center, retrospective study including 52 patients with macroprolactinoma. All enrolled patients were treated with dopamine agonists (cabergoline or bromocriptine). Resistance to dopamine agonists was defined as failure to achieve normoprolactinemia and/or 30% tumor shrinkage. Univariate and multivariate logistic regression analyses were performed to assess predictive factors of dopamine agonist resistance.
Results
Dopamine agonist resistance was observed in 16 patients (31%). Its predictive factors were age at diagnosis <30 years (Odds Ratio (OR):5, 95%-confidence interval (CI):1.39-18.41, $P=0.011$), baseline prolactin level $>$ 7000 µg/l (OR:4.861, 95%-CI:1.145-20.632, $P=0.035$), invasive adenoma (OR:10.263, 95%-CI:1.203-87.550, $P=0.018$), presence of hemorrhagic or necrotic components (OR = 28.5, 95%-CI:3.273-248.175, $P=10\text{-}3$) and tumor size $>$ 40 mm (OR = 7, 95%-CI:1.717-28.545, $P=0.004$). In multivariate analysis, the presence of hemorrhagic or necrotic components was the only independent predictor of resistance. We developed a new score to predict dopamine agonist resistance based on five items including age <30 years (5 points), prolactin level >7000 (4 points), invasive adenoma (10 points), tumor size $>$ 40 mm (7 points) and hemorrhagic or necrotic components (28 points). The total score was 54 points. The mean total score was 45.2 ± 8.4 in patients with dopamine agonist resistance and 17.5 ± 17.3 in patients responding to treatment ($P=10^{-3}$). This score had an area under the ROC curve of 0.902 (95%-CI: 0.816-0.987, $P<10^{-3}$). A total score $>$ 39 points predicted the risk of resistance with a sensitivity of 87% and a specificity of 88%.
Conclusion
We developed in this study a new score for the prediction of dopamine agonist resistance in patients with macroprolactinoma. This new tool would have a decisive impact on surgery timing for better management of macroprolactinomas.

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P156

Incidence of complications of acromegaly 10 years after achieving biochemical control of GH – a single centre retrospective observational study

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Aim
Acromegaly is associated with multiple co-morbidities including diabetes mellitus (DM), obstructive sleep apnoea (OSA), arthropathy, cardiovascular events and malignancies. Early diagnosis and treatment, with an intention to cure or control the growth hormone (GH) exposure can reduce risk of these complications. The aim of this study is to assess the development of acromegaly-related complications amongst patients who have completed at least 10 years of follow up after achieving disease control.
Methods
167 patients who were treated for acromegaly in our tertiary pituitary referral centre (1940 -2012) were included in this retrospective observational study. 81/167 had achieved disease control. 31/81 had been discharged back to the care of the peripheral district general hospitals from which they were referred and hence were not included in the analysis (due to inaccessibility of case files). The case notes, general practice summary care records of 50/81 were subsequently included in the analysis and reviewed for development of any new complications after 10 years of cure and follow up thereafter.

Results
$n=50$: 30 patients remain under follow up and 20 patients had died. The mean duration of follow up was 291 months among patients on follow up and 259 months for those who had died. 21/50 patients did not develop any new complications throughout their follow up. 21/50 developed at least one complication of which 18 developed their complication after 10 years follow-up after cure: HT ($n=9$), DM ($n=7$), malignancy ($n=9$; one patient developed two malignancies), OSA ($n=2$), CCF ($n=3$), TMJ joint pathology ($n=1$) and dementia ($n=1$). [A further 9 patients had developed HT and 5 developed DM within 10 years after control]. On comparing the patients who remained normal ($n=21$) with those who developed complications after 10 years ($n=18$), there was no statistical difference in age at diagnosis (40.7 $\pm$ 14.6 vs. 45.4 $\pm$ 10.2 years), GH at diagnosis (23.4 $\pm$ 36.2 vs. 14.2 $\pm$ 16.5 mg/l), time to achieve control (55 $\pm$ 55 vs. 38 $\pm$ 46 months), modalities to achieve cure, total treatments required to achieve cure or the proportion of macroadenomas (17/21 vs. 13/18)
Conclusions
Our observational analysis of clinical practice demonstrates significant acromegaly–related complications developing during long term follow up of acromegaly despite achieving biochemical control. Though this study did not involve multivariate analysis and adjustment for other relevant risk factors for the comorbidities, it reemphasizes the need for continued monitoring and need for analysis of larger databases

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P157

Various cut-off points for paradoxical increase of growth hormone after glucose load in patients with acromegaly and their clinical implications

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Introduction
Paradoxical increase of growth hormone after glucose load (PR) and its clinical significance remain the focus of researchers. Different cut off points for diagnosis of PR are used in the literature.
Aim
Our aim was to investigate 3 different definitions of PR and their clinical implications.
Material and Methods
We analyzed 116 consecutive patients diagnosed with acromegaly in 2012-2022. We included 89 patients with available pituitary MRI, results of at least 3 GH values in the OGTT and hormonal evaluation before treatment. We used 3 definitions of PR. Definition 1(D1): increase of of GH at any time point of OGTT compared to baseline GH concentration. Definition 2 (D2): increase of at least 25%. Definition 3 (D3): increase of at least 50% occurring earlier than in 120'. For each definition, patients were divided into groups: with PR (PRpos), without PR (PRneg) and compared in terms of: GH concentrations during OGTT, IGF-1 and PRL and their upper limit of normal ratios, tumor volume, Signal Intensity Ratio (SIR) of the tumor and temporal grey matter. Response to SSA was assessed after 3-6 months of presurgical treatment in 69 patients, as the frequency of normalization of IGF1/ULN ratio and IGF1/ULN ratio decrease by $\geq$ 50%. This study was approved by the local Bioethics Committee (1072.6120.72.2020) and is part of statutory research of the Jagiellonian University Medical College (N41/DBS/000407).
Results
According to D1 60.7% of patients were PRpos, PRneg and PRpos differed in median nadir GH (15.05 uIU/ml IQR 23.6 vs. 26.4 I uIU/ml QR 49.2, $P=0.012$) and IGF1/ULN ratio (1.85 IQR 0,46 vs 2.44 IQR 1.05, $P=0.002$). Using D2, PRpos constituted 37.1% of patients. Median fasting GH concentration was higher in PRneg than in PRpos (10.23 ug/ml, IQR 14.19 vs 7.46 ug/ml, IQR 7.96, $P=0.011$). Using D3, 18% patients were PRpos, with no statistically significant differences between groups. The frequency of achieving normalization of IGF1 or decrease by at least 50% did not differ between PRpos and PRneg according to D1, D2, D3.
Conclusions
Even though we used 3 cut off points of PR, we observed no differences in responsiveness to presurgical treatment with SSA between PRpos and PRneg. However, further evaluation is required to understand the significance of PR and precise its exact definition.

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P158

Expression of omentin in the porcine anterior pituitary and action on cell proliferation, cell cycle, and secretion of FSH, LH, PRL, GH, TSH and ACTH

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Background
Omentin, also known as intelectin-1, is a member of the family of adipose tissue-related hormones known as adipokines, that exert anti-inflammatory, anti-atherosclerotic, and cardiovascular protective effects. Omentin expression has been detected in adipocytes as well as in a variety of extra-adipose tissues, including the ovary. Interestingly, omentin expression in the pituitary has been shown to be regulated by pituitary hormones. These observations led us to investigate whether omentin, like the other adipokines, including leptin or adiponectin, regulates pituitary cell proliferation and hormone production. Disturbances of pituitary endocrinology lead to many pathologies. Therefore, the aim of the present study was to investigate i) omentin mRNA and protein expression as well as immunolocalization in the anterior pituitary cells (APc) of sows, ii) in vitro effect of omentin on proliferation, cell cycle, and hormone secretion by pig APc.
Methods
Anterior pituitaries were collected from mature Large White sows on days 2-3, 10-12, 14-16, and 17-19 of the estrous cycle ($n=6$). Omentin mRNA and protein expression as well as immunolocalization in APc were determined by real-time PCR, Western Blot, and immunohistochemistry, respectively. Next, in in vitro experiments, we investigated the time- (4-72 h) and dose- (10-100 ng/ml) dependent effect of omentin on APc proliferation (alamarBlue), cell cycle (flow cytometry), and hormones' secretion (FSH, LH, PRL, GH, TSH, ACTH). Statistical analysis was performed using the Student's t-test, one-way ANOVA, and Tukey's post-hoc test.
Results
Results showed fluctuations of omentin expression in AP during the estrous cycle: mRNA abundance increased from days 10-12 to 17-19, whereas protein concentration was highest on days 10-12, and lowest on days 17-19. We observed colocalization of omentin with FSH and LH in gonadotropes, with PRL in lactotropes, with GH in somatotropes, with TSH in thyrotropes, but not with ACTH in corticotropes. Interestingly, we noted the stimulatory effect of omentin on APc proliferation and an increase in the percentage of cells in the M phase of cell cycle. Additionally, we demonstrated a dose-dependent action of omentin on pituitary hormone secretion: decrease of FSH, increase of LH, GH, TSH, and no effect on PRL and ACTH.
Conclusion
Taken together, our data indicate that omentin, either locally produced or from other sources, may regulate porcine pituitary cells' functions. Funding: National Science Centre, Poland, 2020/37/B/NZ9/01154; Excellence Initiative – Jagiellonian University "Visibility and Mobility Module".

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P159

Mild Autonomous Cortisol Secretion May Be Related To Decreased Thalamic Volume

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Aim
To investigate the volumetric changes in cortical and subcortical deep gray matter (GM) structures and cognitive alterations in patients with mild autonomous cortisol secretion (MACS). We also sought to assess whether the anticipated changes in brain volume and cognitive functions of the patients with MACS differ from the changes in patients with overt Cushing's Syndrome (CS).
Methods
In this cross-sectional study, volumes of the cortex, hippocampus, amygdala, thalamus, caudate, and putamen were examined using 3T magnetic resonance

imaging and a voxel-based morphometry approach in 23 patients with MACS, 21 patients with active CS, 27 patients with CS in remission, and 21 controls. Cognitive functions were assessed using validated questionnaires.
Results
Patients with MACS had smaller volume of left thalamus (F = 3.8, $P=0.023$), left posterior thalamus (F = 4.9, $P=0.01$), left medial thalamus (F = 4.7, $P=0.028$), and right lateral thalamus (F = 4.1, $P=0.025$) than controls. Patients with active CS also had smaller volume of the left thalamus (F = 3.8, $P=0.044$), left posterior thalamus (F = 4.9, $P=0.007$), left medial thalamus (F = 4.7, $P=0.006$), and right lateral thalamus (F = 4.1, $P=0.042$) in relation to controls. Furthermore, patients with active CS and MACS had smaller volumes belonging to the pulvinar and mediodorsal nuclei of the left hemisphere in comparison to controls. Patients with CS in remission showed smaller volumes only in left medial (F = 4.7, $P=0.030$) and right lateral thalamus (F = 4.1, $P=0.028$) when compared with controls. Neuropsychological tests showed no difference between the groups.
Conclusion
MACS may be related to reduced volumes of the whole thalamus and thalamic nuclei similar to patients with overt hypercortisolism.

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P160

Multimodal therapy for the management of an aggressive corticotroph tumour after bilateral adrenalectomy

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Background
Rapid progression of corticotroph tumours can occur after bilateral adrenalectomy for treatment of Cushing's disease. There are currently no guidelines to assist with management of aggressive cases of Nelson's syndrome, particularly after surgery and radiotherapy.
Clinical case
A 53 year old woman presented with classic clinical features of hypercortisolism. Initial investigations showed a markedly elevated 24 hour urine cortisol level of 2426 nmol/day (<250), unsuppressed cortisol after 1mg dexamethasone and ACTH 22.6 pmol/l (0-12). High dose dexamethasone and CRH tests confirmed a pituitary cause of ACTH-dependent Cushing's syndrome. MRI of the pituitary fossa revealed a pituitary macroadenoma, maximum dimension 14 mm, without compression of the optic chiasm but extension into the right cavernous sinus. Surgical resection of the tumour could not be completed due to an intraoperative complication of internal carotid artery rupture and haemorrhagic stroke. Consequently, the patient opted for radiotherapy, achieving clinical remission after 2 years. Tumour regrowth 3 years later necessitated treatment with further radiosurgery (2200 cGy). Laparoscopic bilateral adrenalectomy was eventually performed after 2 years due to further relapse. Postoperative ACTH level was 195pmol/l (0-12). 15 months later she was diagnosed with Nelson's syndrome after significant progression of tumour with a maximum dimension now of 36mm and ACTH level of 2053 pmol/l. Urgent surgical debulking was undertaken via craniotomy. Histopathological evaluation confirmed a pituitary tumour expressing TPIT and ACTH, consistent with a densely granulated corticotroph tumour. Ki67 was elevated around 12-15%. Postoperative ACTH declined to 1190 pmol/l. She completed an 18 month course of temozolamide and capecitabine without progression (ACTH 603 pmol/l). At that point, due to modest tumour growth she received further radiotherapy followed by monthly pasireotide LAR 30mg. ACTH level 9 months after pasireotide is stable at 228 pmol/l, similar to her baseline level before developing Nelson's syndrome.
Conclusion
We employed a multimodal therapeutic approach including surgery, radiotherapy, temozolamide and pasireotide to successfully manage an aggressive corticotroph tumour. There has been adequate tumour control for up to 3 years since development of Nelson's syndrome.

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P161

Neurosarcoidosis Presenting with Panhypopituitarism

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Introduction
Sarcoidosis is a multisystem inflammatory disorder that affects the lungs and the lymph nodes commonly. The involvement of the nervous system in this disease is infrequent with prevalence lower than 10%. The diagnosis could be challenging when the neurologic disease presents in a patient without previously known sarcoidosis.
Case Report
A 39-year-old Caucasian gentleman was brought to the Emergency department with a one week's history of worsening confusion and headache on the background of nine months of intermittent headache, fatigue, weight gain and erectile dysfunction. The non-contrast CT scan of the head showed an infundibular pituitary lesion and he had raised opening pressure (33.5 cm H2O) on lumbar puncture. The cerebrospinal fluid (CSF) studies showed lymphocytic pleocytosis, high protein with normal glucose. He had negative blood cultures, negative CSF BioFire PCR, bacterial and mycobacterial cultures, and negative CSF TB PCR. He also had negative HIV and cryptococcal serology. His serum Angiotensin-Converting Enzyme (ACE) level was 42 U/l (reference range 18 - 55 U/l) and CSF ACE was raised at 4.78 U/l (normal value <1.20 U/l). The patient had panhypopituitarism (central hypothyroidism, hypogonadotropic hypogonadism and hypocortisolaemia) with a mild hyperprolactinaemia of 531 µg/l. He was commenced on oral Hydrocortisone and Levothyroxine was added later. The contrast MRI of the brain showed profuse enhancement of the thickened nodular pituitary infundibulum. There was also widespread profuse enhancement of the leptomeninges particularly around the brainstem and extension of the enhancement along the perivascular spaces of the cerebral hemispheres. The radiologic appearance was suspicious of neurosarcoidosis, and other differential diagnoses were tuberculosis and carcinomatosis. The patient was found to have mediastinal and bilateral hilar lymphadenopathy on CT scan of the chest, abdomen and pelvis. He was commenced on intravenous Methylprednisolone after an ultrasound-guided left inguinal lymph node biopsy showed non-caseating granulamatous changes in keeping with sarcoidosis. The patient improved clinically and he was discharged home to be followed up in the Endocrinology and Sarcoidosis clinics.
Conclusion
Neurosarcoidosis manifests with cranial neuropathy in up to 50% of the cases with the involvement of the hypothalamus and the pituitary gland being infrequent and reported in 2% of the cases only. The diagnosis is generally guided by clinical findings and imaging investigations, supported by extra-neural tissues biopsy. Systemic steroids remain the mainstay of treatment in neurologic disease, as the spontaneous improvement is unlikely to happen.

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P162

An unusual sellar dermoid cyst

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Introduction
Dermoid cysts are rare (0.5% of intracranial tumours). They are best considered a spectrum: from epidermoid cysts containing desquamated squamous epithelium to teratomas containing all three embryonic tissues. Sellar dermoid cysts are even rarer [Orpha.net ID: ORPHA:91351].
Case
A 47-year old white British male was referred following incidental discovery of bitemporal field defect on routine eye test. He was otherwise completely asymptomatic. A 27mm x 24 mm x 27 mm intra-/suprasellar lesion was found on orbital MRI. A pituitary MRI with contrast showed the same mass with a small left lateral extension, superomedial to the proximal middle cerebral artery. The tumour was heterogeneous with areas of high T1 and T2 signal. The bulk of the tumour showed low signal on the fat-suppressed sequences. The suprasellar component displaced the optic chiasm and stretched the pre-chiasmatic segments. The pituitary gland was separate from the tumour. Numerous T1 hyperintense foci were found in the third and left lateral ventricles and in subarachnoid spaces overlying the frontal lobes and the cerebellar hemisphere. The radiological diagnosis was either a craniopharyngioma or a dermoid cyst that has ruptured with intracranial dissemination. Baseline pituitary function was normal: cortisol 477nM/l, testosterone 12 nmol/l, FSH 4.1 IU/l, LH 2.8 IU/l, IGF-1 16.8 nmol/l (ref 7-28), free T4 12 pmol/l, TSH 4.2 mU/l, prolactin 270 mU/l. OCT-RNFL analysis showed deteriorating fibre loss and thinning. Endoscopic transsphenoidal debulking was done. Histology showed keratinous material with a basket weave appearance. Cam5.2 stain showed <20 cells. Reticulin staining and immunohistochemistry for synaptophysin, p53, Ki-67, pituitary hormones and

transcription factors were negative. Visual fields improved. Postoperative endocrine function showed suboptimal cortisol (402 nmol/l) and GH (2.0) on insulin tolerance test. A 3-month postoperative scan showed extensive debulking with a 11 mm residuum. Optic chiasm was decompressed. The patient further scans at 6 monthly intervals. The first showed no change. The second showed increase in the residuum with no immediate pressure on the chiasm. Further proactive surgery is being offered to patient.

Discussion points

- This was an unusual presentation of a very rare condition. Despite rupture of the cyst, the patient was asymptomatic and the field defect was an incidental finding.
- The pituitary function was preserved at presentation despite a large tumour, possibly indicating slow growth over time.
- Histologically, the lesion was closer to the epidermoid end of the spectrum but it is difficult to prognosticate regrowth. Close monitoring is advisable.

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P163

Pituitary apoplexy as the first manifestation of non-functioning pituitary neuroendocrine tumor

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Introduction

Pituitary apoplexy (PA) is a rare but potentially life-threatening complication that may occur in pituitary neuroendocrine tumors (PitNETs). Non-functioning PitNETs (NF-PitNETs), specifically macroadenomas, seem to have a higher risk of apoplexy.

Case description

A 45-year-old male presented to the emergency unit with a one-week history of binocular visual deterioration (blurred vision, diplopia, visual field defect) with left-side predominance, dull headache and nausea. His past medical history was significant for arterial hypertension. The ophthalmological examination showed that visual acuity was limited to hand motion in the left eye with visual field impaired in all directions and a decrease of visual acuity to 0.5 in the right eye without visual field deficits. Vital signs were normal. Apart from the visual impairment, the neurological examination was normal. Initial laboratory tests showed mild hyponatremia (Na^+: 131 mmol/l). A computed tomography of the brain was performed and revealed a haemorrhagic sellar mass with suprasellar extension. The subsequent magnetic resonance imaging confirmed a large pituitary lesion measuring 20x27x29 mm with signs of intratumoral bleeding, compressing and displacing the optic chiasm, compressing posterobasal part of the frontal lobes, and reaching the floor of the third ventricle. The hormonal evaluation showed central hypothyroidism (TSH: 0.761 μIU/ml, FT4: 0.65 ng/dl, FT3: 1.21 pg/ml) and hypogonadotropic hypogonadism (LH: 1.8 mIU/ml, FSH: 4.26 mIU/ml, testosterone: 0.69 nmol/l); the corticotroph axis was preserved (ACTH: 25.3 pg/ml, random cortisol: 25.30 μg/dl). The patient received hydrocortisone intravenously and underwent endoscopic endonasal transsphenoidal surgery. A total resection of the pituitary lesion was achieved. Postoperatively, the ophthalmological deficits improved, however, due to panhypopituitarism, the patient continued oral hydrocortisone. Additionally, levothyroxine, testosterone, and growth hormone replacement therapy were introduced. Due to the transient diabetes insipidus, he required also temporary treatment with desmopressin which was discontinued 12 weeks after the surgery. Pathological examination revealed gonadotroph PitNET with tumor positive staining for FSH, LH and alpha-subunit. The patient is still followed up at our Department.

Conclusions

PA, although being a rare complication of PitNETs, is considered an endocrine emergency, requiring prompt diagnosis and appropriate treatment, especially in cases, when PA is the first manifestation of PitNET. Management of PA should be individualized, however, all patients should receive corticosteroids, regarding the coexistence of adrenal insufficiency. In the case of optic chiasm compression, a neurosurgical intervention should be urgently performed.

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P164

FTO gene polymorphisms and their role in acromegaly

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Acromegaly is characterized by two-fold higher mortality than in the general population. The leading causes of morbidity and mortality in patients with acromegaly are cardiovascular diseases (CVD). Many population-based studies suggest a role of genetic background in CVD and associated metabolic disturbances. In 2007, *FTO* (fat mass and obesity associated) gene polymorphisms were discovered. According to a few studies, the polymorphisms of FTO gene are associated with obesity, as well as with an increased risk of CVD. It has been suggested that the GH / IGF-1 axis may be the mediator of the relationship between the *FTO* gene and BMI. The aim of our study was to determine the relationship of four risk alleles of selected FTO gene polymorphisms: rs1121980 (allele T), rs1421085 (allele C), rs9930506 (allele G), rs9939609 (allele A) with: selected parameters of lipid metabolism and IGF-1 and GH levels in the group of patients with acromegaly compared to control group. We showed that the distribution of the risk-alleles of the analyzed genotypes did not deviate between acromegaly and control group. The data revealed that homozygotes for risk allele carriers as well as only carrier of risk allele have lower IGF-1 (IGF-1 x ULN) concentrations. We did not find any association of *FTO* gene polymorphisms with lipid metabolism in the whole acromegalic group but found these when we analyzed acromegalic patients according to the activity of the disease. In controlled acromegaly group we showed that homozygotes for three risk alleles had lower HDL cholesterol concentration. Homozygotes for the rs1121980-risk allele (allele T) had lower HDL cholesterol concentration than carriers of the CC and CT genotypes ($P\times=\times0.037$). Homozygotes for the rs1421085-risk allele (allele C) had lower HDL cholesterol concentration than carriers of the TT and CT genotypes ($P\times=\times0.035$). Homozygotes for rs993609–risk allele (allele A) had lower HDL concertation than carriers of AT and TT genotypes ($P=0.09$). We observed a similar situation for total cholesterol and LDL cholesterol. What is important to note, we did not observe this association in the control group. Conclusion: There is an association between *FTO* gene polymorphisms and lipids metabolism suggesting *FTO* gene polymorphisms may be associated with higher CVD risk in patients with acromegaly. In addition, there is an association between *FTO* gene polymorphisms and IGF-1 concertation implying *FTO* gene polymorphisms may influence/modify IGF-1 synthesis. Further investigation on a larger scale is required to provide more precise evidence.

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P165

Longer surveillance period needed for Ectopic ACTH secretion and Cushing's syndrome – two unusual cases

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Ectopic Cushing's syndrome is a rare condition accounting for 10–20% of all cases of ACTH-dependent Cushing. Neuroendocrine tumours (NETs), mainly bronchial carcinoids and small cell lung cancer, are the most frequent causes of ectopic ACTH secretion(1). Here we report two challenging cases with long duration of surveillance and monitoring.

Case 1

A 42-year-old lady with a florid Cushing syndrome underwent bilateral adrenalectomy in 2002. An IPSS in 2001 failed to demonstrate a central to peripheral ACTH gradient suggesting an ectopic ACTH secretion. Serial whole-body gallium 68 DOTATATE PET CT over a decade failed to reveal any tracer avid lesion. CT CAP did not identify any pathology. Since 2012, her ACTH level continued to rise and peaked at 3800 ng/l. Despite thorough radiological evaluation, the source remained unlocalised. In 2016, 16 years after her initial diagnosis, her CT CAP revealed a 13 mm right perihilar nodule with a positive FDG-PET in the perihilar region. She underwent right middle lobectomy. Histology showed a typical bronchial carcinoid with positive ACTH stain and low proliferation index (Ki-67 1%). Post operative ACTH level was 12 ng/l and she is in remission.

Case 2

A 31 years old lady was diagnosed with ectopic Cushing's syndrome and required bilateral adrenalectomy in 1990 to ameliorate hypercortisolism. Surveillance imaging with CT and octreotide scans over the period showed two right lung nodules with marginal interval growth. The case was discussed in the lung MDT in 2006 and 2014. The nodules were not amenable for surgery. Her ACTH level during this time was between 1000 and 2800 ng/l. In 2015, the nodules increased in size with growth noted in proximity to the main vessels and bronchi. It was then decided to proceed with a right lung wedge resection. Histology confirmed bronchial carcinoids and stained positive for ACTH. The ACTH level fell from peak 2210 to 24 ng/l postoperatively with spontaneous remission of Cushing's syndrome.

Conclusion

We present two uncommon cases of ectopic ACTH secretion caused by bronchial carcinoid, which took nearly two decades for localisation. The cases highlight the fact that identifying the source of ectopic secretion is always challenging due to their small size and unpredictable anatomical location. It is of paramount importance for regular follow up with surveillance imaging.

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Doege-Potter Syndrome, a case report

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Introduction
2 to 3% of the causes of hypoglycemia in the population without diabetes mellitus correspond to tumors of cells other than islets. Below is a rare case of hypoglycemia related to a pleural tumor.
Clinical case
A 65-year-old woman with arterial hypertension, psychiatric treatment for confusion and behavioral changes of 6 months of evolution, palpitations and night sweats, loss of 20 kg of weight, several admissions to the emergency room, until her hospitalization due to alteration of the sensory, where severe hypoglycemia is found. She denies using hypoglycemic agents, corticosteroids, and alcoholism. Physical examination: Diminished vesicular murmur in the middle and lower left lung fields. Laboratory tests: Plasma glucose: 30 mg/dl, serum insulin: less than 1 Uu/ml, C peptide: 0.17 ng/ml, anti-insulin antibodies: 1.8 negative, the rest in normal range including cortisol, normal thyroid, renal and hepatic function. Chest CT: left pleural tumor of 30 x 20 cm in the left hemithorax. Biopsy: spindle cell proliferation. Tumor excision and histology: well-defined stromal neoplastic proliferation, without atypia, suggestive of an intense, diffuse, cytoplasmic CD34+ solitary fibrous tumor. Desmin, pancytokeratin AE1/AE3 and S 100 negative, ki67 10%, resolved hypoglycemia after surgery.
Discussion
Doege- Potter syndrome is a rare cause of hypoglycemia, characterized by solitary fibrous tumors that are associated with hypoglycemia of non-islet cell tumors of the pancreas (NICTH). These are epithelial of mesenchymal tumors, of various locations, that produce IGF2, which bind to insulin receptors, increasing peripheral glucose consumption, decreasing glycogenolysis and gluconeogenesis. In general, hypoglycemia is fasting with confusional symptoms; as the case of our patient; in which it is confused with a psychiatric picture. Decreased peptide C and decreased insulinemia make it necessary to think about NICTH. In half of the cases, hypoglycemia precedes the discovery of tumors, as stated. Hypoglycemia is not related to aggressiveness or tumor size. Random IGF2 levels may be normal; in this case IGF2 dosing was not possible. Complete resolution of hypoglycemia after surgery supports the diagnosis of the syndrome. In conclusion, Doege- Potter syndrome, a rare and potentially reversible entity, should be evaluated in the differential diagnosis of hypoglycemia in the population without diabetes.

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P167

Somatostatin analogue treatment is associated with lack of progression of pNETs <20mm in size in patients with MEN1

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Introduction
Pancreatic neuroendocrine tumours (pNETs) are the main cause of mortality in patients with multiple endocrine neoplasia type 1 (MEN1). The CLARINET study demonstrated that somatostatin analogue treatment improved progression free survival in patients with enteropancreatic NETs but little is known about the role of SSA in preventing progression of pNETs in MEN1 (1). Many centres have started using SSA treatment in MEN1 patients with enlarging pNETs or tumours >15 mm. This is current practice in our centre.
Objective
This observational study examined the effectiveness of somatostatin analogue (SSA) treatment in preventing progression of pNETS in MEN1.
Methods
Using our database of MEN1 patients, electronic patient records were individually reviewed to document the radiological, biochemical and clinical behaviour of pNETs over time. Patients were treated with SSA if tumours had documented growth, were > 15 mm in size or were associated with metastases. We compared pNET size/ growth in patients treated and untreated with SSA (overwhelmingly lanreotide autogel 120 mg 4 weekly).
Results

Demographics

	Total MEN1 cohort
n	57
Gender	37F: 20M
Age (y)	45 (16)
PNETs documented	44 (12 surgical)
Deceased (n)	8
Mean age of death, y (range)	59 (41-84)
SSA use (%)	35.1
Metastases N (%)	4 (7.02)
Surgical intervention? N (%)	16 (28.1)
Other Rx (n)	Peptide receptor radiotherapy (PRRT) ($n=2$)

Conclusion

Included patients treated with SSA compared with untreated patients

	MEN1 cohort with pNETs on SSA	MEN1 cohort with pNETs not on SSA
n	20	12
Gender	12F: 8M	8F:4M
Age (y)	42.2 (12.9)	41.6 (17.6)
Deceased (n)	3	2
Mean age of death (y)	56	51
Cause of deaths	Metastatic pNET x2, metastatic gastrinoma	ACC, metastatic pNET
Surgical intervention? (n)	3	1
PNET size (mm)(SD)	15 (8)	8 (4)
Stable disease	11	8
Progression	1	1
Improvement	4	0
Data unavailable	4	3
Duration of SSA use	4- 120 (mean: 48)(SD 24)	N/A
Duration of total surveillance (mths)	61.9 (25.2)	34.8 (24.6)
SEs reported	Minimal reporting-GI Symptoms, GB sludge, ?pancreatitis	N/A
Other Rx	1 patient had PRRT	

These data indicate that mean duration of 4 years SSA treatment is associated with stable size or reduction (20%) in pNETs averaging 1.5 cm in patients with MEN1. Multi-centre collaboration, including comparison of a larger untreated cohort would clarify the effectiveness of SSA preventing progression on pNETs in MEN1.
Reference
Caplin ME, *et al*. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med.* 2014;371:224–233.
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P168

Quantitative assessment of the signal intensity of somatotropin pituitary tumors and its clinical implications in consecutive newly-diagnosed patients with acromegaly

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Introduction
Somatotroph Pituitary Neuroendocrine Tumor's (sPitNET) signal intensity in T2-weighted MR images (SI) was reported as prognostic marker for tumor's aggressiveness and poor response to 1st generation somatostatin analogs (SSA). Tumors are arbitrary divided into 3 groups: hyperintensive (HYPER), isointensive (ISO) and hypointensive (HYPO).
Aim
Our aim was to quantitatively assess SI of sPitNETs and investigate its clinical implications.
Patients and methods
116 consecutive patients newly diagnosed with acromegaly between 01.01.2012 and 31.12.2022 at the Department of Endocrinology, Jagiellonian University Medical College were evaluated. Patients with available coronal T2-weighted pituitary MRI images were included. Exclusion criterion was tumor's cystic

component preventing from SI assessment. Finally, 67 patients were in the analysis. SI of the solid part of sPitNETs, grey and white matter of the temporal lobe were measured. Patients were divided into 3 groups: HYPER, with SI higher than grey matter, ISO with SI higher than white matter, but lower than grey matter and HYPO with SI lower than white matter. Baseline and nadir GH after glucose load; IGF-1 and upper limit of normal range for age, sex ratio (IGF%ULN) before and after SSA treatment, tumor volume measured by manual delineation of Volume of Interest (TV), and baseline GH concentration to TV ratio (GH/TV) were compared. This study was approved by the Bioethics Committee (1072.6120.72.2020) and is part of statutory research (N41/DBS/000407).
Results
Median TV was 1.38 cm3 (IQR 4.51) for HYPER, 1.83 cm3 (IQR 6.44) for ISO and (0.58 cm3 IQR 0.73) for HYPO ($P=0.005$). TV was higher in HYPER than in HYPO ($P=0.04$) and in ISO than in HYPO ($P=0.04$), with no differences between HYPER and ISO($P=1.0$). Differences in baseline GH, nadir GH in OGTT and IGF1%ULN before and after treatment with SSA, were not significant. GH/TV ratio was higher in HYPO (43.64 uIU/ml*cm^3 IQR 48.35) than in HYPER (11.78 uIU/ml*cm^3 IQR 15.75) ($P=0.037$) and higher in HYPO than in ISO (20.38 uIU/ml*cm^3; IQR 32.57) ($P=0.005$), with no significant differences between HYPER and ISO ($P=1.0$)
Conclusions
Both HYPER and ISO were larger than HYPO. HYPO may seem more biochemically active than HYPER and ISO tumors. In our cohort, no statistical differences were found between HYPER and ISO tumors. Whether HYPER and ISO tumors constitute two separate groups in terms of clinical significance, requires further research.

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P169

Lymphocytic Hypophysitis – many faces of the same disesase. Watchful waiting could be suggested therapeutic approach in majority of patients

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Introduction
Clinical manifestation of hypophysitis depends on presence of hormonal abnormalities and/or enlargement of pituitary structures. Both the diagnosis and treatment still remain challenging. Hormonal replacement is the basic therapy, while steroids are the first-line treatment in case of mass related symptoms. The course of the disease varies from spontaneous remission to atrophy of the pituitary gland.
Aim
To characterize and sum up clinical/hormonal/radiological findings and therapeutic approach in patients with probable lymphocytic hypophysitis.
Methods
A retrospective analysis of 12 patients (9W/3M) with probable lymphocytic hypophysitis hospitalized in our Department (2015-2022) was performed. Clinical, laboratory and imaging findings were assessed. The study is a part of a project "Assessment of the health condition of patients with hypopituitarism in Poland" (grant N41/DBS/000408).
Results
Mean age at diagnosis was 49.2 years (48.2 for W, 52.0 years for M). Headaches and diabetes insipidus were the first manifestation in 7/12 and 3/12 cases, respectively, while 2/12 patients presented with clinical symptoms of adrenal insufficiency. In one patient hypocortisolism was transient, in the second case reassessment is difficult due to inhaled and oral steroids used by patient in asthma exacerbations. 5/12 patients were diagnosed with diabetes insipidus (one temporary) and gonadal axis dysfunction was detected in 5/12 cases (one transient). Central hypothyroidism was found in 4/12 patients – in all cases permanent. Probable GH deficit (based on lower insulin-like growth factor 1 concentration) was suspected in 5/12 patients (one transient). One patient had no hormonal abnormalities. Magnetic resonance (MR) revealed thickened pituitary stalk (max. 11 mm) in all but one cases; in two – lack of the posterior lobe signal. In one patient the area of inflammation within the anterior pituitary lobe was described. The hormonal substitution was administered appropriately to the deficits; due to the severe headaches 3 patients were given steroids (2 in intravenous pulses, one orally) with subsequent reduction in the frequency and severity of complaints and stable/improved image of pituitary area in the control MR. One woman was operated due to the progression in the pituitary tumor size and mass effect-related symptoms – histopathological examination confirmed lymphocytic hypophysitis. In the remaining 8/12 patients watchful waiting approach allowed to obtain hormonal and radiological stabilization/improvement.
Conclusions
Non-specific, transient characteristic of the symptoms and hormonal deficits cause difficulties in establishing proper diagnosis. The treatment may vary depending on the clinical and hormonal status. Further research and long term observation might help in better understanding of the disease.

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P401

Mortality in acromegaly diagnosed in the elderly in Spain is higher in women compared to the general Spanish population

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Context
There is no data on mortality of acromegaly diagnosed in the elderly.
Objective
To compare clinical characteristics, GH-related comorbidities, therapeutic approaches and mortality of patients diagnosed before or after 2010 and to assess overall mortality compared with the general Spanish population.
Setting
Spanish tertiary care centers.
Design, Patients, and Methods
Retrospective evaluation of 118 patients diagnosed with acromegaly at or above the age of 65. Kaplan-Meier curves were constructed to trace survival, and Cox proportional hazard models were used to assess the risk factors associated with mortality. We also compared mortality with that of the Spanish population by using age- and gender-adjusted standardized mortality ratios (SMR)
Results
No differences were found in first-line treatment or biochemical control, between both periods except for faster biochemical control after 2010. Twenty-nine (24.6%) patients died, without differences between groups, median of follow-up 8.6 years [103, (72.3) months]. Overall SMR was 1.02 (95% CI: 0.57–1.54), [0.60 (95% CI: 0.35–1.06) for men] and [1.80 (95% CI: 1.07–2.94) for women]. The most common cause of death was cardiovascular disease (CVD).
Conclusions
The mortality in patients with acromegaly diagnosed in the elderly was no different between both periods and there was no overall SMR difference from the general Spanish population. However, the SMR was higher in women. As CVD is the leading cause of mortality, it seems advisable to initiate an intense CVD protective treatment as soon as acromegaly is diagnosed, particularly in women, in addition to tight acromegaly control in order to prevent excess mortality.

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P402

Treatment Patterns in Acromegaly: Analysis of Real-World US Insurance Claims from the MarketScan® Database

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Background
Medical treatment for acromegaly (characterized by excess growth hormone [GH] production) includes somatostatin receptor ligands (SRLs), dopamine

agonists (DAs), and GH receptor antagonists (GHRAs). However, recent real-world United States (US) treatment evaluations are few. We present treatment patterns for patients receiving medications for acromegaly (1/1/2010–31/7/2022).
Methods
De-identified data were extracted from MarketScan®, a US health insurance claims database. Eligible patients were ≥18-years-old at diagnosis; receiving monotherapy or combination therapy (≥2 treatments overlapping for >3 months) for ≥90 days without treatment gaps; had ≥2 claims associated with acromegaly; with data ≥3 months before and ≥6 months after diagnosis/first treatment claim (earlier date). Outcomes were: demographic characteristics; treatment frequency by line of treatment (LOT) and changes between LOTs (Sankey plot); treatment persistence for first LOT (LOT 1) monotherapies (Kaplan–Meier estimator); and treatment up-/downtitration (≥30% dose change, for octreotide long-acting release [OCT] and lanreotide depot [LAN]). Biochemical control values were unavailable.
Results
Of 882 patients, 50.1% were female; mean age at diagnosis was 48.6 years (standard deviation 13.6 years). Among patients, 59.4% had 1 LOT, 23.1% had 2 LOTs, and 17.5% had 3 LOTs. Most common LOT 1 medication class was first-generation SRLs: OCT (27.7%), LAN (21.1%). Other LOT 1 classes: DAs (cabergoline; 34.5%), GHRAs (pegvisomant; 10.5%). In LOT 1, only 7 patients received second-generation SRL pasireotide and no patients received oral octreotide. Most patients initiated treatment with monotherapies (94.6%). Among LOT 1 monotherapies, GHRAs had the longest median persistence (pegvisomant; 24.8 months; 95% confidence interval [CI]: 16.59–32.49 months; $n=93$), followed by first generation SRLs (OCT and LAN; 20.0 months; 95% CI: 16.98–23.87 months; $n=430$). DAs had the shortest persistence (cabergoline; 14.4 months; 95% CI: 12.23–16.82 months; $n=304$). Of patients receiving OCT or LAN, 67.6% had ≥1 dose uptitration; 45.0% had ≥1 dose downtitration.
Conclusions
Despite consensus guidelines recommending DA monotherapy for few select patients with acromegaly, our real world analysis found that approximately one third of patients initiated treatment with this class with the shortest persistence. OCT and LAN monotherapies were also commonly used as LOT 1 and had longer persistence. GHRAs, the class with the longest persistence, were not common monotherapy in LOT 1, possibly due to not targeting pituitary adenomas directly. Interestingly, only 5% of patients initiated treatment with combination therapies. Recommendations for individualized therapy should consider medication persistence and real-world treatment patterns.

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P403

Bilateral Inferior Petrosal Sinus Sampling and Utility of Maximum Stimulated Petrosal Sinus ACTH to Baseline ACTH ratio in Adrenocorticotropin-dependent Cushing's Syndrome

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Methods
The diagnosis of Cushing's Syndrome (CS) was made as per the prevalent endocrine society guidelines. CS patients with serum ACTH>15 pg/ml were considered as ACTH-dependent CS. Baseline ACTH (both inferior petrosal sinuses and peripheral) values were obtained, and since 2014, stimulated ACTH values (5 and 10 minutes post one unit iv vasopressin) were obtained as standard protocol. Prolactin corrected ACTH ratios were additionally being calculated since 2016. The highest central to peripheral ACTH gradient >2 in baseline samples (bC:P), >3 in samples after vasopressin stimulation (sC:P), and >0.8 in PRL-corrected ratios (pC:P) was used as reference value indicative of Cushing's Disease (CD). An inter-petrosal gradient >1.4 was considered to be suggestive of an adenoma located on the side of the petrosal sinus with the higher ACTH concentration.
Results
Of the 51 patients with ACTH-dependent CS who underwent BIPSS, four patients with incomplete data, one patient with unilateral petrosal sinus catheterization, one patient with Cortisol Resistance Syndrome were excluded from the analysis. Mean age of our cohort was 37.5 years, with 77.8% females. 39 patients had CD, while six had ectopic CS. bC:P>2 ($n=45$) demonstrated 92.3% sensitivity, 83.3% specificity, 97.3% PPV and 62.5% NPV, while sC:P>3 ($n=31$) demonstrated 96.3% sensitivity, 100% specificity, 100% PPV and 80% NPV to diagnose CD. pC:P>0.8 ($n=20$) improved the sensitivity and NPV to 100%, with a 75% specificity and 94.1% PPV. On ROC analysis, cut-point ratio of 2.55 for bC:P value gave a sensitivity of 89.7% and specificity of 100% (AUC=0.964); sC:P ratio of 2.95 had 96.3% sensitivity and 100% specificity (AUC=0.991); 0.93 for pC:P ratio provided a sensitivity of 93.8% and specificity of 100% for diagnosis of CD (AUC=0.984). Maximum-stimulated petrosal sinus ACTH to baseline petrosal sinus ACTH ratio of <1.11 provided a 100% sensitivity, while a ratio >1.75 provided 100% specificity towards diagnosis of CD. 71.4% (10/14) patients with left sided adenoma, and 85% (17/20) patients with right sided adenoma were correctly lateralised on BIPSS. In patients whom adenoma was detected on pituitary MRI, 66.7% (6/9) were correctly lateralised to the left side, and 94.1% (16/17) to the right side.
Conclusions
BIPSS provides high sensitivity and specificity to diagnose CD. Vasopressin stimulation improves the sensitivity and specificity, while prolactin correction improves the sensitivity of BIPSS, as compared to baseline ratios. Maximum-stimulated petrosal sinus ACTH to baseline petrosal sinus ACTH ratio can be additionally used, especially in CD patients suspected of false negative localization.

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P404

Prevalence of transient and permanent diabetes insipidus after transsphenoidal pituitary surgery: A systematic review and meta-analysis

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Introduction
Patients undergoing transsphenoidal pituitary surgery (TPS) may develop water balance disorders post-operatively, with diabetes insipidus (DI) being the most common. Nonetheless, data on the prevalence of post-operative DI are not consistent necessitating a systematic review of the literature.
Aim
To estimate the prevalence of DI following TPS in patients with pituitary adenomas (PAs), craniopharyngiomas and Rathke's cleft cysts (RCCs) by performing a systematic review and meta-analysis of published studies which have provided clear criteria of DI diagnosis.
Methods
Extensive literature search of Medline, Embase and Cochrane Library between 01/01/2000 and 31/12/2020 was conducted. Prevalence of postoperative DI, effect size (ES) and 95% confidence intervals (CIs) were estimated from each study and pooled using random effects meta-analysis model.
Results
From a total of 11,627 studies, 54 were finally included. Overall, 22% of patients who underwent TPS developed post-operative DI (ES 0.22; 95%CI, 0.17-0.27). In particular, DI was diagnosed in 19% (ES 0.19; 95%CI, 0.15-0.23), 61% (ES 0.61; 95%CI, 0.49-0.72) and 44% (ES 0.44; 95%CI, 0.27-0.61) of patients with PAs, craniopharyngiomas and RCCs, respectively. Data specifically on rates of transient and permanent post-operative DI were provided in 40 studies; prevalence of transient and permanent DI in total population was 17% (ES 0.17; 95%CI, 0.13-0.21) and 3% (ES 0.03; 95%CI, 0.02-0.05), respectively. Further subgroup analyses revealed prevalence of post-operative transient and permanent DI of 16% (ES 0.16; 95%CI, 0.12-0.20) and 2% (ES 0.02; 95%CI, 0.02-0.03) in patients with PAs, 31% (ES 0.31; 95%CI, 0.24-0.39) and 30% (ES 0.30; 95%CI, 0.22-0.39) in patients with craniopharyngiomas, as well as 35% (ES 0.35; 95%CI, 0.16-0.57) and 14% (ES 0.14; 95%CI, 0.06-0.23) in patients RCCs, respectively. Prevalence of DI was also affected by the diagnostic criteria used in each study. When hypotonic polyuria was sole criterion of diagnosis, post-operative DI was reported in 18% of patients (ES 0.18; 95%CI, 0.12-0.26), whilst in studies where both hypotonic polyuria and hypernatraemia were required as diagnostic criteria, prevalence was 29% (ES 0.29; 95%CI, 0.18-0.42). In those studies where diagnosis was based on desmopressin administration requirement, 26% of cases developed post-operative DI (ES 0.26; 95%CI, 0.09-0.48).
Conclusions
Overall, 22% of patients undergoing TPS for the above tumours will develop post-operative DI. This resolves in the majority of PAs and remains permanent in a significant number of craniopharyngiomas and RCCs. Diagnostic criteria for post-operative DI remain variable affecting the reported prevalence of this condition.

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P405

The TRH test is a valuable diagnostic test in central hypothyroidism with low T4

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Objective
To evaluate the value of the thyrotropin-releasing hormone (TRH) test in the diagnosis of central hypothyroidism (CH) in patients with pituitary disease.
Methods
Systematic evaluation of 368 TRH tests including measurements of TBG corrected thyroxine ($T4_{corr}$), baseline TSH (TSH_0) and fold and absolute TSH increase (TSH_{fold}, $TSH_{absolute}$) in patients with pituitary disease.
Results
Patients diagnosed with CH ($n=40$) show comparable TSH_0 (P-value 0.57) but lower $T4_{corr}$ (P-value 0.001) and TSH_{fold} response (P-value 0.001) compared to patients without CH. In 54% (44 of 81 cases) of the patients with low $T4_{corr}$, the CH diagnosis was rejected based on a high TSH_{fold}. In these cases, a spontaneous increase and normalisation in $T4_{corr}$ (62 to 74nmol/l, P-value 0.001) was observed during the follow-up period (7.7 years, SD $\pm$4.9). Two of the 44 patients (4.5%) were started on replacement therapy due to spontaneous deterioration. In patients with normal $T4_{corr}$ ($n=258$), no patients were diagnosed with CH based on the TRH test. Patients diagnosed with CH reported significantly more symptoms of hypothyroidism (P-value 0.006), although, symptoms were reported in most patients with pituitary disease. There were only mild adverse effects related to the TRH test except for one case (0.3%) with a pituitary apoplexy.
Conclusions
The TRH test is a useful and safe diagnostic test but could be reserved for patients with pituitary disease and a low T4. Approximately 50 % of patients with a low $T4_{corr}$ were considered to have normal pituitary thyroid function based on the TRH test results.

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P406

Somatotroph Pituitary Neuroendocrine Tumors (Pitnets)/Adenomas Expressing Steroidogenic Factor (SF1)

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Rationale and aim
A recent pangenomic study documented a subset of somatotroph mostly GNAS-wildtype PitNET/adenomas co-express steroidogenic factor 1 (SF1). Aim of our study was to investigate clinical and molecular features of a cohort of these tumour subtype.
Study sample
We identified 20 cases of SF1-expressing somatotropinomas out of 173 (11.6%) operated via transsphenoidal endoscopic approach in 3 referral Pituitary Centers patients. Pre- and post-operative biochemical and imaging, histopathological data, and follow-up were available.
Results
The cohort included 10 male and 10 female patients with a mean age at surgery of 50.2$\pm$14.9 years (range 27-70.4; median 47.1). Eighteen patients (80%) presented with clinical and biochemical features typical of acromegaly. Mean tumor maximum size was 17.2 $\pm$ 7.5 cm; 17 (85%; 10 males) were macro PitNET/adenomas, of which 9 (45%) showed cavernous sinus invasion, and 2 (10%) with sphenoid sinus invasion. Resection was total in 14 patients (70%) and 6 had subtotal resection (30%) . At follow-up, acromegaly relapsed in 4 (20%). Molecular analysis identified a pathogenic mutation of *NOTCH* (p. N335K; VAF17%) and *GNAS* (p. R201C; VAF61%) in a male aged 50.8 years, with a non-invasive tumour and post-surgical disease relapse. No mutations were found in *KRAS*, *BRAF*, *TP53*, *PIK3CA*, *CDKN2A*, *TERT*, *PTEN*, *FBXW7*, *EP300*, *CASP8*, *AIP* and *USP8*.
Conclusions
Patients with somatotroph PitNET/adenomas expressing SF1 typically present with large and invasive tumours, with overt clinical and biochemical features of acromegaly. Most of the cases are GNAS-WT. The incidence of tumour recurrence and disease relapse is similar to the known relapse rate in acromegaly patients.

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P407

TGFβ1 and activins as new therapeutic targets for the treatment of dopamine-resistant prolactinomas

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Background
Pituitary tumours are commonly benign adenomas, accounting for 10-15% of all intracranial neoplasms. Among functioning pituitary tumours, prolactinomas are the most frequently observed in the clinic (about 40%). Dopamine, acting through the dopamine type 2 receptor (Drd2), is the main inhibitor of lactotroph proliferation and prolactin secretion, therefore, these tumours are usually treated with dopaminergic agonists with a high efficiency. However, there is a subset of prolactinomas (15 and 20%) that do not respond to this treatment, named dopamine agonist resistant prolactinomas, which represent a major challenge for clinical management, because up to date, no alternative treatments have been found. Transforming growth factor β1 (TGFβ1) and activins are known inhibitors of lactotroph cell proliferation and prolactin secretion.
Aims
Study the role of TGFβ1 and activins in normal and tumoral pituitaries, in 3 animal models of prolactinomas.
Hypothesis
We postulate that, due to the inhibitory action on lactotroph functions exercised by the intra-pituitary members of the TGFβ-family, these factors represent novel targets to develop alternative treatments for resistant prolactinomas.
Results
We demonstrated, in 3 different animal models of prolactinomas, the Drd2 knock-out mice, the estrogen-treated rat and the hCGβ overexpressing mice, that:
1. Pituitary TGFβ1 activity, several components of the TGFβ1 system (LTBPs, TβRII, local activators), as well as activin and activin-receptors expression are reduced in prolactinomas vs normal pituitaries;
2. *in vivo* pharmacological treatments that recover pituitary TGFβ1 activity reduce the hyperprolactinemia and counteract the tumour growth;
3. TGFβ1 activity and activin expression are higher in male pituitaries (sex differences: protective factors?),
4. Ovariectomy in animal models of prolactinoma recovers pituitary TGFβ1 activity and activin expression preventing prolactinoma development.

Conclusion
These findings open new possible therapies in treatment for prolactinomas, especially in those that are resistant to dopaminergic drugs.

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P408

Pooled analysis from two osilodrostat Phase III studies in Cushing's disease (LINC 3 and LINC 4): Clinical improvements according to urinary and late-night salivary cortisol levels

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Introduction
In two Phase III studies (LINC3, NCT02180217; LINC4, NCT02697734), osilodrostat, (potent oral 11β-hydroxylase inhibitor), provided rapid, sustained reductions in mean urinary free cortisol (mUFC) and late-night salivary cortisol (LNSC), alongside improvements in clinical signs of hypercortisolism and health-related quality of life (HRQoL), in Cushing's disease (CD) patients. mUFC and LNSC are recommended for monitoring treatment response. We assessed whether patients with both controlled mUFC + LNSC experienced greater improvements in clinical signs of hypercortisolism and HRQoL, compared to control of mUFC alone.
Methods
LINC3 comprised a 48-week (W) core phase, including an 8W randomised-withdrawal period. LINC4 included a 12W, double-blind, placebo-controlled period followed by 36W of open-label osilodrostat. Both studies had an optional extension. mUFC (mean of 2–3 samples; normal range [NR] 11–138 nmol/24h) and LNSC (one sample; NR $\leq$ 2.5 nmol/l) were measured by liquid chromatography-tandem mass spectrometry. Changes in cardiovascular/metabolic-related parameters, physical manifestations of hypercortisolism and HRQoL were assessed in the pooled population by mUFC/lNSC control status: both controlled mUFC + LNSC (mUFC $\leq$ upper limit of normal [ULN] + LNSC $\leq$ ULN), controlled mUFC (mUFC $\leq$ ULN + LNSC>ULN) and both uncontrolled mUFC + LNSC (mUFC>ULN + LNSC>ULN). Patients with controlled LNSC (mUFC>ULN + LNSC $\leq$ ULN) were not analysed as few patients had LNSC control without UFC control. Patients in core and extension phases with both mUFC and LNSC assessments were included. Placebo treatment periods were excluded.
Results
Of evaluable patients at baseline (n = 160), 136 (85.0%) had both uncontrolled mUFC + LNSC. At W48 (n = 133) and W72 (n = 111), respectively, 59 (44.4%) and 54 (48.6%) patients had both controlled mUFC + LNSC, 49 (36.8%) and 44 (39.6%) had controlled mUFC, and 19 (14.3%) and 11 (9.9%) had both uncontrolled mUFC + LNSC. Patients with both controlled mUFC + LNSC had greater percentage improvements from baseline to W72 in cardiovascular/metabolic-related parameters than patients with controlled mUFC or both uncontrolled mUFC + LNSC, respectively: fasting plasma glucose, –5.0%, –4.8%, 1.9%; glycated haemoglobin, –5.1%, –4.8%, –1.3%; weight, –6.5%, –6.5%, –4.5%; waist circumference, –7.2%, –6.3%, –4.9%. Physical manifestations of hypercortisolism generally improved from baseline to W72 irrespective of mUFC/lNSC control. Patients with both controlled mUFC + LNSC or controlled mUFC had the greatest improvement from baseline to W72 in HRQoL.
Conclusions
Patients with both controlled mUFC + LNSC or controlled mUFC had the greatest improvements in cardiovascular/metabolic-related parameters and HRQoL. Improvements in most physical manifestations of hypercortisolism were observed irrespective of mUFC/lNSC control. Data are limited by small patient numbers in some groups. Both mUFC and LNSC normalisation can improve long-term treatment outcomes in CD patients.

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Inflammatory infiltrate in wild-type and non-wild-type GNAS somatotropinomas

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Introduction
Somatotropinomas are benign pituitary tumors with heterogeneous biological and clinical behavior. The tumor microenvironment (TME) is an environment generated by the interaction between tumor cells and the host immune system. It affects both the behavior of the tumor and the outcome of the therapy. The GNAS gene encodes the alpha subunit of G proteins associated with hormone receptors such as TSH, PTH, GHRH, FSH/lH, ACTH. Mutation of this gene has been associated with more aggressive forms of acromegaly. We aim to investigate the presence of CD3+, CD20+, CD138+, CD4+, CD8+, CD68+ cells in the tumor inflammatory infiltrate and their correlation with GNAS mutations.
Material and methods
A retrospective, monocenter study was conducted on 36 acromegaly pts included according the following criteria: 1) age >18 at the diagnosis of acromegaly, 2) availability of tumor sample. Pts with history of radiotherapy of head/neck within 10 years before pituitary surgery, with immune-related disease were ruled out.
Results
Thirty-six patients (23 females) entered the study. Macro-adenomas were identified in 23 cases (12 with cavernous sinus invasion). The median value of tumor infiltrating CD3+ lymphocytes was 30/HPF (IQR: 41.7, range: 7-122), of CD20+ lymphocytes was 2.5/HPF (IQR: 2.75, range: 0.5-12), of CD138+ was 6.5/HPF (IQR: 7.75, range: 1-44), of CD4+ lymphocytes was 5/HPF (IQR: 5.5), of CD8+ lymphocytes was 21/HPF (IQR: 29.5) and of CD68+ macrophages was 50/HPF (IQR: 30). CD68+/CD4+ ratio was 2.4 (IQR: 4.8). Four patients carried GNAS mutations. The number of CD3+, CD20+, CD138+, CD4+, CD8+, CD68+ was similar among GNAS wild type and not-wild type patients.
Conclusion
According to our preliminary data, GNAS mutation do not modify TME in somatotropinomas.

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Impact of Surgery or Medical Treatment with the Selective Glucocorticoid Receptor Modulator Relacorilant on Hypercoagulopathy in Patients with Cushing Syndrome

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In patients with Cushing syndrome (CS), hypercoagulability represents a significant concern, leading to elevated risk for thrombotic events. After curative surgery, hypercoagulability persists for several months; CS treatment guidelines recommend anticoagulation therapy for $\leq$ 3 months. In patients with Cushing disease, hemostatic parameters may even worsen after surgery, independent of surgical outcome; improvements begin ~3 months after successful surgery (Casonato *et al. Blood Coagul Fibrinolysis* 1999). This transient worsening may be due to increased inflammation—cortisol levels, and hence cortisol's anti-inflammatory effects, decrease after successful surgery, leading to increased coagulation cascade activity, which normalizes over time. We evaluated the impact of surgery or treatment with the selective glucocorticoid receptor modulator relacorilant on the coagulation state in patients with CS in a retrospective, longitudinal, monocentric, surgical cohort study and an open-label phase 2 study of relacorilant (NCT02804750). In the surgical study, coagulation markers were assessed in 30 patients before curative surgery and during remission. In the relacorilant study, patients received relacorilant 100–200 mg for 12 weeks or relacorilant 250–400 mg for 16 weeks; coagulation markers were assessed in 34 patients. In the surgical study, baseline mean 24-hour urinary free cortisol (UFC) was 615.6 mg/day (by immunoassay; 2.1× upper limit of normal [ULN]); mean and median time to hemostasis assessment after remission were 6.2 and 6 months. Significant mean changes from baseline were observed in activated partial thromboplastin time (aPTT; +2.0 seconds, P = 0.031), factor VIII (fVIII; 24.2%, P = 0.044), and von Willebrand factor (vWF; 20.6%, P = 0.018); platelet

count was unchanged. In the relacorilant study, baseline mean UFC was 211.9 mg/day (by tandem mass spectrometry; 4.2× ULN). Similar to the surgical study, significant mean changes from baseline to last observed visit were reported in aPTT (+1.5 seconds, $P=0.046$), fVIII (-18.9%, $P=0.022$), and platelet count ($68.8*10^9$/l, $P<0.0001$); vWF was unchanged. Significant improvements in other coagulation factors (eg, fIX and fX) were seen in patients with abnormal baseline values. These studies showed that coagulation markers in patients with CS improve 6 months after curative surgery, and relacorilant treatment may have similar effects after 3–4 months. Transient increases in fVIII immediately after surgery were absent with relacorilant, where negative mean changes from baseline were seen throughout the study. This is presumably due to the less abrupt reduction of cortisol activity with relacorilant compared to surgery. Relacorilant's effects on hypercoagulopathy support further investigation of preoperative use and in patients with CS who are ineligible for surgery.

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P411

Usefulness of the short version of the acute octreotide test for prediction of first-generation somatostatin receptor ligands response in acromegaly: a validation study with the ACROFAST cohort

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We previously described a short version of the acute octreotide test (sAOT) for predicting somatostatin receptor ligands (SRLs) response in patients with acromegaly[1]. In the present work, we prospectively reassess the sAOT ability to identify SRLs response in patients from the ACROFAST study using the current GH standards and control criteria and we also correlate sAOT values with E-cadherin tumor expression.

Methods

Patients from the ACROFAST study evaluated with the sAOT before receiving any medications and treated with first generation somatostatin analogues. Response to SRLs was evaluated at 6 months of medical treatment in 47 participants: those patients whose IGF1 was <3SDS were considered *responders* and those with IGF1≥3SDS, *non-responders*. Additionally, E-cadherin immunohistochemistry expression was investigated in 22/43 patients. The value of GH 2 h after the administration of 100 mg of octreotide subcutaneous (GH_{2h}) was evaluated according to the IGF1 response and to the E-cadherin expression, in order to generate cut-off GH values predicting SRLs response.

Results

47 patients (30 responders, 17 non-responders) were analyzed. GH_{2h} was higher in non-responder patients (5.04 vs 1.17ng/ml; $P<0.01$). ROC analysis for predicting non-response with GH_{2h} cut-off showed an Area Under Curve of 0.832. A GH_{2h} value of 4.3ng/ml was the best cut-off for non-response prediction, with a Positive Predictive Value of 92% (Sensitivity 35%; Specificity 97%). The cut-off for GH_{2h} of 1.4ng/ml showed the highest ability to identify responders with a Negative Predictive Value for non-response of 92% (Sensitivity 94%, Specificity 73%). Patients with E-cadherin expression tumors presented a lower GH_{2h} compared with tumors with low or no E-cadherin expression (1.29 vs 5.69ng/ml; $P<0.01$).

Conclusions

The sAOT is a good predictor tool for assessing SRLs treatment response and correlates with E-cadherin tumor expression, thus being useful in clinical practice in patients with acromegaly for the medical therapeutic decision-process.

Reference

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P412

Copeptin levels increase in response to both insulin-induced hypoglycemia and arginine but not to clonidine – data from GH-stimulation tests

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Background

The differential diagnosis of the polyuria-polydipsia syndrome is challenging. The water-deprivation test is the current gold standard, but the test is cumbersome, and the diagnostic performance is poor. Copeptin, which is a split product of the vasopressin pre-propeptide, appears to be a robust biomarker in the circulation and a promising tool for the diagnosis of patients with polyuria and polydipsia, especially when measured in conjunction with intravenous infusion of arginine. With this study we aimed to clarify underlying mechanisms of copeptin secretion.

Methods

Using a cross-sectional study-design, we included patients referred to Aarhus University Hospital with suspicion of growth hormone deficiency, who underwent arginine ($n=16$), insulin tolerance test ($n=12$) or clonidine ($n=8$) stimulatory tests. Baseline copeptin was measured and repeated at 60, 105 and 150 minutes.

Results

Copeptin level increased significantly from baseline to 60 min after arginine ($P<0.01$) and ITT ($P<0.01$). By contrast, copeptin level tended to decrease after clonidine stimulation ($P=0.14$). Arginine and the ITT induced a similar response in copeptin level from baseline to 60 min ($P<0.01$).

Conclusion

The present data support that arginine infusion and the ITT induce a similar increase in plasma copeptin level after 60 min. Clonidine tended to decrease copeptin levels. We hypothesize that abrogation of somatostatin-induced copeptin-suppression could be a possible explanatin.

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Sleep Disorders And Osas Risk in Patients with Prolactinoma: A Single Center Experience

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Purpose

Dopaminergic system is implicated in the development of sleep disorders, and dopaminergic agents are used in clinical practice to treat daytime sleepiness and sleep disorders. The present study aimed at investigating the effects of hyperprolactinemia and its control with dopamine-agonists (DA) on sleep quality, excessive daytime sleepiness (ESS) and risk of obstructive sleep apnea syndrome (OSAS) in prolactinomas.

Methods

A single-centre study was conducted from July to December 2022: 44 patients with prolactinoma (23 M, 21 W, aged 46,4±14,42 yrs), including 22 with

macroprolactinoma, 20 with microprolactinoma and 2 with empty sella, were sex- and BMI-matched with 80 healthy controls (32 M, 48 W, age 34,8 ± 11yrs). In all participants, 3 questionnaires were administered to investigate sleep disorders (Pittsburgh Sleep Quality Index, PSQI, normal score <5), daytime sleepiness (Epworth Sleepiness Scale, ESS, normal score <10) and OSAS risk (Berlin Questionnaire, BQ, normal score less than 2 categories). In all participants, height, weight and BMI were recorded. In patients, tumour size at diagnosis, PRL at evaluation, treatment duration (TD), CAB dose (CD), and fasting glucose and insulin were evaluated.

Results

Between patients and controls no significant difference was found in the prevalence of sleep disturbances, ESS and OSAS risk. According to patient age, a significant difference ($P=0.028$) in OSAS risk was found in older patients (age> 56y) as compared to other quartiles. Based on sex, BMI, PRL, TD and CD, no significant difference was found in the prevalence of sleep disturbances, ESS and OSAS risk. In patients, tumour size and BMI were significantly higher in men than in women ($P<0.001$; $P= 0.043$). In male patients, PSQI scores directly correlated with tumour size ($r=0.45$; $P= 0.029$), whereas ESS scores directly correlated with tumour size ($r=0.533$; $P=0.009$), BMI ($r=0.51$; $P=0.012$), PRL ($r=0.457$; $P=0.028$).

Conclusions

The results of the current study did not confirm an association between sleep disturbances, ESS and OSAS risk and treatment with DA in patients with prolactinomas, but ESS was associated with PRL levels. OSAS risk appeared to be influenced by age and daytime sleepiness by BMI. Interestingly, sleep quality was associated with tumour size, suggesting that the long-term effects of chiasm compression on sleep-wake rhythmicity, observed especially in patients with large pituitary tumours, might negatively impact sleep quality.

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Assessment of adrenal axis function in patients with PROP1 mutation – longitudinal observation

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Introduction

Mutation in PROP1 gene is the cause of different forms of pituitary dysfunction. The assessment of the functioning of the adrenal axis still raises the most doubts.

Aim& methods

A retrospective longitudinal (mean 35 years, SD 16.24) analysis of 32 patients (19W/13M, including 5 families and sporadic cases) with PROP1 mutation was performed to define the optimal diagnostic approach in evaluation of adrenal axis. In the study morning cortisol and ACTH were assessed in 27/32 patients as well as tests with 1 ug of recombinant ACTH and 100 ug of CRH were conducted in 22/32 and 18/32 patients, respectively. Project grant number N41/DBS/000408).

Results

26/32 were diagnosed with adrenal gland insufficiency, not all family were affected. In majority of patients the disease was detected later than deficits in other hormones (mean delay 17.75 years). In 4 cases it was found at initial diagnosis of pituitary dysfunction. The youngest and oldest patients were diagnosed at the age of 7 and 60, respectively. 3 patients presented with transient adrenal insufficiency – the hydrocortisone substitution was withdrawn due to retesting in adulthood. The average dose of hydrocortisone is 15,7 mg/day. The mean morning cortisol and ACTH concentrations were 6,62 ug/dl (SD 5.12, min./max. 1,09/19.35 ug/dl) and 20.18 pg/ml (SD 7.49, min./max. 8.6/49 pg/ml), respectively. Test with ACTH confirmed adrenal dysfunction in 14/22 patients, while test with CRH was positive in 13/18 patients. In 14 patients tests findings were compatible. All patients with abnormal Synacthen test had positive CRH test results as well. CRH revealed adrenal insufficiency in 3 additional patients with normal ACTH stimulation test or correct morning cortisol. Surprisingly, significant rise in ACTH concentration was observed in the CRH stimulation test with mean maximum value 100,7 pg/ml (min./max. 26/260 pg/ml), both in adrenal sufficient and insufficient patients suggesting other than ACTH deficit mechanism of adrenal insufficiency.

Conclusions

Adrenal insufficiency in patients with PROP1 mutation may occur at any age. Usually is detected later than other hormonal deficits, some patients may present with transient abnormalities, some retain its proper function throughout whole life. Morning cortisol is not an sufficient marker of adrenal condition; stimulation tests are commonly required and test with CRH seems to be the most adequate. In the view of ACTH increase after stimulation further studies are needed to understand the underlying mechanism and find the best diagnostic algorithm for patients with pituitary function deterioration caused by PROP 1 mutation.

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Synchronous multiple pituitary neuroendocrine tumors (PitNETs) consisting of a null cell and PIT-1 lineage adenomas: a peculiar acromegalic case report

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Pituitary adenomas constitute the third most common intracranial neoplasm. Adenoma cells either express no hormone (null cell adenoma) or hormones of different cell lineage. About 1% of pituitary adenomas shows a plurihormonal expression pattern, which may either be attributed to one cell lineage or rarely to different cell lineages. In addition, the development of separate pituitary adenomas may be observed in 0.5–1.5% of surgical specimens and in up to 10% of autopsy cases. These lesions are termed synchronous multiple pituitary neuroendocrine tumors (PitNETs) and are traditionally known as difficult to be detected at preoperative imaging investigation. Synchronous multiple PitNETs clinical manifestations depend on the histological subtypes. Specifically, null cell adenomas are invasive at the time of presentation and have an aggressive clinical course with short progression-free survival. We present a case of a 45-years old woman in which, following the diagnostic investigations for a suspected Guillain-Barrè syndrome, a 13 mm pituitary lesion was found on brain MRI images. On T2-weighted images, the lesion was described as iso-hypointense in the peripheral edge and hyperintense in the central portion with mild compressive effect on the pituitary stalk and optic chiasm. Despite the absence of clinical acromegalic features, the blood tests showed an increased baseline GH and IGF-1 levels (4.9 ng/ml and 401 ng/ml respectively) and the lack of GH suppression during OGTT test (GH nadir 3.9 ng/ml) confirming the diagnosis of acromegaly. Transsphenoidal surgery was performed with a regular post-operative course, with disease remission confirmed by biochemical and radiological investigation at one- and three-months follow-up. At histology, a synchronous multiple PitNETs were found, consisting of a PIT-1 lineage and a null cell adenomas. The former was a mixed somatotroph-lactotroph PitNET with a low mitotic and proliferative index (<3 mitoses for 10 HPF, Ki67<3%). On the other hand, the latter was characterized by spindle cells, negative for all pituitary hormones and transcription factors (TTF-1, T-PIT, SF1, PIT1 and GATA3) with focal p53 overexpression and a high proliferative index (Ki67 5-6%). Given the ambiguous histological nature of this component, the case was discussed collectively, deposing for possible aggressive behavior of the null cell adenoma. In conclusion, this is a rare and incidentally discovered case of a synchronous multiple PitNETs, in which the absence of acromegalic features and the histological characterization may suggest an aggressive and rapidly growing neoplasm, that require careful clinical-radiological post-operative follow-up.

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Treatment, complications and mortality of Cushing's Disease: twenty-year report from a referral Centre

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Context

Cushing's disease (CD) is rare condition burdened by several systemic complications that in turn increase mortality. The main goal of CD treatment is

to promptly reduce cortisol excess, but whether remission can revert cortisol-related complications and guarantee a normal life expectancy remains debated.
Aim
To assess the prevalence of cortisol-related complications and mortality in a large monocentric cohort of CD patients followed at our centre.
Materials and methods
We reviewed clinical charts of patients with CD diagnosed between December 2001 and December 2021. Biochemical features, CD treatments history, comorbidities and deaths were recorded.
Results
126 CD patients, with a median follow-up of 10 years were included. Median age at diagnosis was 39 years, with a prevalence of females gender (F:M = 3:1), microadenomas (80.5%) and mild to moderate cortisol excess (77.5%). At last follow-up, 78/126 (61.9%) patients were in remission irrespective of previous treatment strategies. All but one patients with active CD at last follow-up were on medical treatment, achieving normalization of urinary free cortisol and circadian rhythm in about 75% and 25%, respectively. Remission proved a significant improvement in all cardiovascular (CV) comorbidities ($P<0.05$). Patients presenting multiple comorbidities (at least 3) at last follow-up had increased CV complications ($P=0.013$). CV events were also more frequent in older patients ($P=0.003$), smokers ($P=0.02$) and in persistent cases ($P=0.044$). Most of thromboembolic (TE) and infective events occurred during active disease. Older age ($P=0.04$) and dis-glycaemia ($P=0.035$) were related to TE events; whereas no predictors of infective complications were identified. CV events were the most frequent cause of death. SMR was increased in patients with persistent disease at last follow-up (SMR 4.99, 95%CI [2.15; 9.83], $P<0.001$), whilst it returns comparable to that of general population after remission (SMR 1.66, 95%CI [0.34; 4.85], $P=0.543$). This latter finding was confirmed irrespective of timing and number of treatments performed to achieve remission. Younger age at diagnosis ($P=0.005$), a microadenoma at first imaging ($P=0.002$) and remission status at last follow-up ($P=0.027$) increased survival. Conversely, an elevated number of CV risk factors at last follow-up ($P=0.0057$), especially arterial hypertension, increased mortality.
Conclusions
active CD patients present a poor survival outcome, but disease remission can restore life expectancy. This result seems independent of timing and modalities used to achieve remission. Nevertheless, adequate monitoring and management of persisting CD-related comorbidities is of the outmost importance to reduce both CV events and mortality

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A negative association between growth hormone secretion and inflammation in adult patients with non-functioning pituitary mass

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Background
Growth hormone (GH) deficiency, which causes visceral obesity and non-alcohol fatty liver disease, increases cardiovascular event risks. High-sensitivity C-reactive protein (hs-CRP), an inflammatory marker associated with increased cardiovascular risk, reportedly decreased after GH supplementation in GH-deficient patients, however, the association between GH secretion and inflammation remains unclear.
Patients and Methods
We retrospectively investigated the association between GH secretion assessed using a GH-releasing peptide-2 (GHRP-2) test and serum hs-CRP level in the patients with non-functioning pituitary neuroendocrine tumor (NF-PitNET) and Rathke's cleft cyst (RCC). Patients with severe renal insufficiency, active inflammatory and malignant diseases, and a history of pituitary surgery, and under GH supplementation therapy were excluded.
Results
Among 171 patients (100 NF-PitNET and 71 RCC), 55 (32%) presented severe GHD. Serum hs-CRP levels were significantly higher in the patients with severe GHD than those without (754 [393-1330] vs 249 [113-537] ng/ml, $P<0.001$) and significantly correlated with peak GH response to GHRP-2 ($r=-0.50$, $P<0.001$). Peak GH response to GHRP-2 significantly estimated the hs-CRP levels independent of the atherosclerotic and metabolic parameters and other anterior hormone secretions ($\beta = -0.334$, $P = 0.001$). Severe GHD was significantly associated with high hs-CRP (> 1000 ng/ml) (adjusted odds ratio, 2.55; 95% confidence interval 1.15-5.70). In the 60 patients who received pituitary surgeries, the postoperative changes in peak GH response to GHRP-2 ($\beta = -0.320$, $P = 0.025$) significantly estimated those in serum hs-CRP levels independent of other anterior hormone secretions.
Conclusions
The negative association between GH secretion and serum hs-CRP levels suggested an important role of impaired GH secretion in the increased cardiovascular risks through the development of inflammation.

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Search for new biomarkers of adult growth hormone deficiency metabolic syndrome: a comprehensive overview of a four peptides analysis

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Adult growth hormone deficiency (aGHD) is characterized by an altered metabolic profile and increased cardiovascular risk. Neudesin is a newly discovered protein mainly secreted from adipose tissue and brain, under evaluation for its possible activity as negative regulator of energy expenditure. Liver expressed antimicrobial peptide (LEAP)-2 is a competitive antagonist of ghrelin on its receptor. Spexin is a polypeptide related to the galanin-kisspeptin family, secreted along with insulin by pancreatic beta cells with insulin secretion blunting effect. Given the role played in metabolism and energy balance, plasma evaluation of the four peptides was performed and any possible relationships between them and metabolic/anthropometric parameters were evaluated. Thirty-eight patients were included: 18 aGHD patients (7 females and 11 males, aged 59.7 ± 2.6 years, BMI 30.2 ± 2.2 kg/m^2); 20 healthy controls (12 females and 8 males, aged 47.1 ± 2.5 years, BMI 24.1 ± 0.9 kg/m^2). aGHD was diagnosed by a GHRH plus arginine test. They were evaluated for glucose and insulin, HOMA and QUICKI index, total/lDL/HDL cholesterol, triglycerides, uric acid and IGF-1. Plasma neudesin, LEAP-2, ghrelin and spexin were measured by ELISA, according to manufacturers' protocols. Fat mass percentage was evaluated by DXA. Data were expressed as Mean $\pm$ SEM. AGHD patients showed significantly higher HOMA index and triglycerides, and lower HDL cholesterol than controls. Age and BMI significantly differed between aGHD patients and controls; however, no correlation between peptides and age or BMI was detected in aGHD patients, controls, or the overall enrolled population. Fat mass percentage was significantly higher in aGHD than controls, as expected (44.41 ± 3.15 vs 32.2 ± 3.64). Neudesin plasma levels (ng/ml) were significantly higher in aGHD patients than in controls (2.83 ± 0.37 vs 1.55 ± 0.12). Ghrelin plasma levels (nM) were significantly lower (0.91 ± 0.08 vs 1.07 ± 0.09), LEAP-2 (nM) significantly higher (5.19 ± 0.42 vs 3.68 ± 0.49) and consequently LEAP-2/ghrelin ratio significantly higher (6.29 ± 0.84 vs 3.51 ± 0.53) in aGHD patients than in healthy controls. Spexin levels (ng/ml) were similar in the two groups (aGHD 1.17 ± 0.21 vs controls 1.25 ± 0.10). A significant and strong direct correlation between neudesin and LEAP-2 was found both in aGHD patients and in the overall analyzed population. A significant direct correlation between neudesin and uric acid in aGHD patients was also found. Negative correlations were found between neudesin plasma levels and plasma concentrations of glucose and HDL cholesterol. On the contrary, neudesin plasma concentrations appeared positively correlated with the plasma levels of triglycerides. Finally, in the whole population, a significant direct correlation between neudesin and fat mass percentage was pointed out.

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Reference intervals for soluble alpha klotho and the impact of biological variables

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Background
Alpha klotho is a transmembrane protein that regulates calcium metabolism. Its soluble portion has been linked to endocrine functions. We have recently shown high concentrations of serum soluble alpha klotho (sαKL) in active acromegaly. There is limited information about regulation of sαKL secretion. We aimed to gain insight about sαKL as a potential biomarker for H-related diseases.
Methods
SαKL was measured by ELISA (IBL, Hamburg, Germany) in healthy adults (A, $n=890$, ~120 subjects/decade) to calculate a reference interval for sαKL. It was compared to concentrations of patients with non-functional pituitary adenomas (NFPA, B, $n=18$) or prolactinomas (C, $n=66$). Moreover, we evaluated the potential impact of biological variables on sαKL concentrations.
Results
The reference interval (2.5-97.5 centile) for sαKL in healthy adults was 152-1303 pg/ml (median: 673 [IQR: 543-846]). SαKL was not different in NFPA (A vs. B, p>0.05), but higher in prolactinoma (902 [754-1228]; A vs. C, $P<0.0001$). SαKL in males was slightly lower than in females (651 [537-815] vs. 687 [546-881], $P=0.01$). As expected, IGF-I and IGFBP 3 significantly differed between age decades, while sαKL mainly differed between individuals <40 as compared to $\square 70$ years ($P<0.05$ for all comparisons). SαKL exhibited a weak negative correlation with age, BMI, waist-hip-ratio, ($r_s=-0.30$, -0.13, -0.12, respectively, $P<0.001$ for all) and a positive correlation with estimated glomerular filtration rate and IGF-I ($r_s=0.11$, 0.31, respectively, $P<0.001$ for all). These correlations were remarkably weaker than those observed for IGF-I and IGFBP 3. There was no correlation between sαKL and IGFBP 3 or parameters of glucose, liver and calcium metabolism ($P>0.05$ for all), while IGF-I and IGFBP 3 correlated with glucose and calcium metabolism. SαKL was slightly lower in individuals after $>$ 12h of fasting and on use of isolated estrogen ($P<0.05$ for all).
Conclusions
We provide a reference interval for sαKL from a large cohort of healthy adults. Furthermore, we show that many biological variables correlate only weakly with sαKL. Fasting and oral estrogens are associated with slightly lower sαKL, perhaps through induction of hepatic GH-resistance which was already described for IGF-I. In prolactinoma patients, sαKL concentrations were slightly higher, but within the reference interval. This could be due to the somatotropic activity of prolactin. Overall, our findings support the concept that sαKL might be a specific, GH-sensitive biomarker, and less impacted by biological variables as compared IGF-I and IGFBP 3. Our data could facilitate the use of sαKL as a biomarker in GH-related diseases.

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Italian guidelines for the management of prolactinomas

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Aim
This guideline (GL) is aimed at providing a reference for the management of prolactin (PRL)-secreting pituitary adenoma in non-pregnant adults.
Methods
For each question, the panel identified potentially relevant outcomes, which were then rated for their impact on therapeutic choices.
Results
The present GL provides recommendations about the roles of pharmacological and neurosurgical treatment for the management of prolactinomas. We recommend cabergoline (Cab) vs bromocriptine (Br) as the first-choice pharmacological treatment, to be employed at the minimal effective dose capable of achieving the regression of clinical picture. We suggest that medication and surgery are offered as suitable alternative first-line treatments to patients with non-invasive PRL-secreting adenoma, regardless of size. We suggest Br as an alternative drug in patients who are intolerant to Cab and are not candidates for surgery. We recommend pituitary tumor resection in patients 1) Without any significant neuro-ophthalmologic improvement within two weeks from the start of Cab, 2) Who are resistant or do not tolerate Cab (or other dopamine-agonist drugs, DA), 3) Who escape from previous efficacy of DA, 4) Unwilling to assume a chronic DA treatment. We recommend that patients with progressive disease notwithstanding previous tumor resection and ongoing DA should be managed in a multidisciplinary team with specific expertise in pituitary diseases with a multimodal approach that includes repeated surgery, radiotherapy, DA, and, possibly, temozolomide.
Conclusions
The present GL is directed to endocrinologists, neurosurgeons, and gynecologists working in hospitals, in territorial services or in private practice, and to general practitioners and patients.

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Factors Affecting Quality of Life in Patients with Acromegaly: Single Center Experience

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Objective
Despite treatment, the quality of life in patients with acromegaly remains lower than in the healthy population due to the classical findings and complications related to the disease. Therefore, in the follow-up of acromegaly, evaluation of quality of life along with symptoms and biochemical parameters is recommended. The aim of our study was to evaluate the quality of life, anxiety and depression status of our acromegaly patients and to assess the factors affecting these.
Material and Methods
Ninety acromegaly patients (46 females, 44 males) followed in our center were included in the study. After completing the demographic information form, four questionnaires were applied to the patients; General Quality of Life Questionnare (EQ-5D-3L), Acromegaly Quality of Life Questionnare (AcroQoL), Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI). Information about disease status, current complications, treatment were obtained from patient records.
Results
The mean age of the study group was 48 11.02 years. The median scores of AcroQoL, BDI, BAI, EQ-5D and EQ-5D/VAS were 76.7 % (61.93-85.5), 10.5 (4.75-15.25), 9 (4-18), 0.779 (0.69-1) and 80 (70-90) respectively. Female patients had higher BAI, BDI scores ($P<0.001$, $P=0.003$ respectively) and lower EQ-5D and AcroQoL scores ($P=0.004$, 0.002 respectively). Patients with elementary school/no education had lower AcroQoL, EQ-5D, EQ-5D/VAS scores and higher BDI score than high school/university graduates ($P=0.002$, 0.027, 0.037, 0.006 respevtively). There was no significant difference between patients who received replacement therapy for hypopituitarism and those who did not, but the AcroQol and EQ-5D, EQ-5D/VAS score was significantly better and BAI score was worse in those who received gonad replacement therapy ($P=0.019$, 0.015, 0.02, 0.013 respectively). In addition, patients with diabetes insipidus had higher BDI scores and lower EQ5D scores ($P=0.025$, 0.05 respectively). There was a negative correlation between follow-up time and AcroQol scores ($r=$-0.209, $P=0.048$). Educational status negatively correlated with BDI and BAI scores ($r=$-0.284, $P=0.007$; $r=$-0.267, $P=0.011$), and were positively correlated with EQ-5D, EQ-5D/VAS and AcroQol scores ($r=0.291$, $P=0.005$; $r=0.287$, $P=0.006$; $r=0.361$, $P<0.001$).
Conclusions
Gender and educational status are the main determinants of quality of life, depression and anxiety in acromegaly patients.

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Effects of a GLP-1 agonist on consumption of alcohol in patients treated for smoking cessation

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Introduction
Alcohol use disorder AUD causes high socio-economic costs and has a detrimental impact on health globally, being considered a key risk factor for non-communicable diseases. In Switzerland, four substances are currently approved for treatment of AUD, with varying effects. Taking into consideration the complex nature of the disease and the heterogeneity of affect patients, it becomes evident that there is need for new treatment targets. A body of preclinical studies provide evidence for the attenuating effects of GLP-1 agonists on addictive behavior in rodents and non-human primates. Furthermore, a few studies have shown a link between GLP-1 receptors and reward related processes in humans, however clinical data are scarce and results remain inconclusive.
Methods
This is a secondary analysis of the SKIP study, a double-blind, randomized, placebo-controlled trial to evaluate treatment with the GLP-1 agonist dulaglutide (Trulicy®) as a new therapy for smoking cessation. In the present analysis, the primary objective was to assess differences in alcohol consumption after 12 weeks of treatment with dulaglutide compared to placebo in smokers willing to quit smoking. We selected patients out of the cohort ($n=255$) who consumed alcohol at baseline and completed 12 weeks of treatment ($n=151$). The independent effect of dulaglutide on alcohol consumption was analysed by fitting a multivariable generalized linear regression model with quasipoisson distribution and adjustment for baseline alcohol intake.
Preliminary Results
One hundred and fifty-one patients (placebo $n=75$, dulaglutide $n=76$) were included in the primary analysis. Baseline patient characteristics were well balanced between groups. The median [IQR] age was 42 [33, 53] years with 61% ($n=92$) females. At baseline, patients in both treatment groups consumed 3 [IQR 2, 7] standard glasses of alcohol per week on average. At week 12, patients in the dulaglutide group drank an estimated 29% less (baseline alcohol intake adjusted IR$r=0.71$; 95% CI 0.52, 0.97; $P=0.04$) than patients in the placebo group.
Conclusions
These results suggest that participants treated for smoking cessation drink significantly less alcohol after 12 weeks of treatment with dulaglutide compared to placebo. Our data thus contribute to the growing evidence promoting the use of GLP-1 agonists in treatment of addictive disorders.

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Immune profile in acromegalic patients and the impact of the current medical treatment. Resultsfrom the PROMISE study

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Context
Acromegaly is associated with several metabolic and cardio-respiratory comorbidities, with a relative increase in the last years of cancer mortality. Although the GH/ IGF-1 axis has long been supposed to play a role on immune modulation, immune function in acromegaly is poorly known.
Objective
This observational, prospective, single site, pilot study (NCT05069324) aims to analyse peripheral blood mononuclear cells (PBMCs) subpopulations in acromegalic patients and the potential impact of disease control and different medical treatments.
Methods
Twenty-nine patients with active acromegaly (16M and 13F, mean age 51.3 ± 15.6 years) (ACRO) have been enrolled - 4 naïve, 15 on somatostatin analogs (SSA), 10 on pegvisomant monotherapy or combined with SSA - and compared with 25 sex- and age-matched control subjects (CTRL). Anthropometric, metabolic, and hormonal parameters were recorded along with full quantification of PBMCs (monocytes, lymphocytes, and natural killer/NK cells) by flow cytometry. Monocytes (MONO) were further divided into classical (CD14++ CD16-), intermediate (CD14+CD16+) and non-classical (CD14+CD16++). NK cells were also divided into $CD56^{dim}$ and $CD56^{bright}$, which are respectively characterized by a relatively higher naturally cytotoxic activity or cytokine production. Data are expressed as median (IQR) and non-parametric tests were used for statistical analysis.
Results
Compared with CTRL, ACRO had higher levels of fasting blood glucose ($P=0.001$), HbA1c ($P=0.001$) and BMI ($P=0.015$) and a higher prevalence of cardio-metabolic comorbidities. ACRO had significantly lower total MONO [197 (101-355) vs 334 (279-411) cells/μL, $P=0.049$], with a lower percentage of intermediate [2.9 (1.5-4.8) vs 7.3 (5.5-10.4) %, $P<0.001$] but an increased percentage of non-classical MONO [7.9 (5.3-11.37) vs 1.7 (1.0-3.3) %, $P<0.001$]. Moreover, ACRO had a significantly lower total number of NK [123 (62-261) vs 279 (198-410) cells/μL, $P=0.003$], with a lower percentage of $CD56^{bright}$ [0.8 (0.1-2.9) vs 7.8 (6.9-10.2) %, $P<0.001$] but a higher percentage of $CD56^{dim}$ [99.0 (97.3-99.8) vs 91.3 (88.2-92.8) %, $P<0.001$], and similar T and B-lymphocytes. No significant differences were found according to disease control and medical treatment in ACRO.
Conclusions
To the best of our knowledge, this is the first evidence of a peculiar immunological fingerprint in acromegaly, with a reduced number of MONO and NK cells and an

imbalance of immune innate cells subsets. No major impact of disease control and treatment was found in this series. This suggests that immune function should be further investigated in acromegalics, particularly in view of their higher oncological risk.

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The acro-TIME score: a new clinical, pathological and immune integrative approach to early identify acromegaly patients resistant to treatment with first generation somatostatin ligands

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Somatotropinomas are benign pituitary tumors, with a heterogenous biological and clinical behavior. Tumor microenvironment reflects the interaction between tumor cells and the host immune system and may regulate tumor behavior and therapy outcome. We develop a scoring system that includes clinical, pathological and immune markers to early identify fg-SRLs resistant acromegaly pts. 43 acromegaly pts were included according the following criteria (1) first line treatment with surgery, (2) post-surgical fg-SRLs therapy (3) availability of tumor sample. Pts not-naïve to acromegaly therapies before surgery, with history of radiotherapy of head/neck within 10 years before pituitary surgery, with immune-related disease were ruled out. Eighteen pts (41.9%) were fg-SRLs resistant: 14 were females (77.8%), with a median age of 36.5 (IQR:13) and with cavernous sinus invasion in 12 cases (66.7%). At histological examination, Ki-67 was $<$ 1.5% in 17 cases (39.5%). The SSTR2A Volante scores were 0-1 in 5 cases (11.6%) and 2-3 in 38 cases (88.4%). Tumour-infiltering CD4+ lymphocytes was 4.9/HFP (IQR: 8), CD8+ lymphocytes was 11/HFP (IQR:14) and CD68+ cells was 60/HFP (IQR:69). The ratio CD68+/CD8+ cells was 5.2 (IQR: 5). We analysed 18 clinical, pathological and immune features as possible predictors of fg-SRLs response. Fg-SRLs resistance was associated to age at acromegaly diagnosis $<$37 years (AUC: 0.72 OR: 2 95%IC: 1.1-4 $P=0.04$), cavernous sinus invasion (OR: 9.3 95%IC:1.4-61 $P<0.001$), Ki-67>1.5% (OR: 3.2 95%IC:1.2-13.1 $P=0.04$), score 0-1 of SSTR2A (OR: 2.7 95%IC: 1.7-4.1 $P=0.03$), ratio CD68+/CD8+ cells $<$5.7/HPF (AUC: 0.709 OR: 4.9 95%IC:1.2-19.2 $P=0.03$) and persistence of post-surgery residual tumour (OR: 2.5 95%IC:1.3-4.7 $P=0.004$). These variables were analysed in a logistic regression model, yielding a beta coefficient of 3.7 for age $>$37 years; of -3 for cavernous sinus invasion; of -0.2 for Ki-67>1.5%; of 20 for SSTR2A score 2-3; of -0.9 for CD68+/CD8+cells ratio $>$5.7/HFP; and of -0.9 for persistence of post-surgery residual. We assigned a score to each covariate proportional to its beta coefficient, yielding a cumulative score for each patient. The score values ranged from 18.5 to 24 in cases responsive to fg-SRLS and from -5.5 to 21.5 in fg-SRLs resistant cases. A score $<$19 was chosen as cut-point to identify fg-SRLs resistance (AUC: 0.059 $P<0.001$ 95%IC: 0.0-0.126). A score $<$19 was associated to fg-SRLs resistance in 84.6% of cases ($P<0.001$ OR: 3.7 95%IC:1.7-6.7). This new score integrates clinical, pathological, immunological data and may predict resistance to fg-SRLs and the need of second line treatments.

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Longitudinal multiomics characterization of paired primary and recurrent aggressive pituitary tumors from the same patient reveals genomic stability and transcriptomic and epigenetic heterogeneity with metabolic pathways alterations

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Pituitary tumors (PT) represent 20% of all intracranial neoplasms. Some behave aggressively, growing rapidly and invading surrounding tissues, with high recurrence rates and are frequently resistant to conventional therapies. We performed exome and transcriptome sequencing, as well as methylation profiling of **primary and recurrent PT of the same patient**. The cohort consisted of patients with GH- and gonadotropin-producing PT and a patient with an ACTH carcinoma. We sought genome evolution as well as transcriptomic and methylomic changes trough time, trying to identify molecular markers of recurrence. We performed scRNAseq to identify tumor cell populations. Compared to the primary PT, recurrent lesions showed less than 5% genomic changes in the SNV profile. The gonadotrophinomas did not show common variants between patients or between primary and recurrent lesions. The ACTH-carcinoma showed USP8, TP53 and EGFR variants in both tumor samples, but no genomic changes between tumors despite a Ki67 of 80% in the recurrent lesion. A GH-tumor showed an AIP variant with high genetic heterogeneity. No CNV between the primary and recurrent tumors were observed. Regardless of their lineage, all PT showed different degrees of transcriptomic and methylomic heterogeneity between the primary and the recurrent lesions. Primary and recurrent tumors clustered separately from each other but together among themselves. Interestingly the differentially expressed and methylated genes in gonadotropin-producing PT are related to fatty acid biosynthesis and metabolism, GPI-anchor biosynthesis, and other metabolic pathways. ACTH-carcinoma differs significantly from the silent corticotrope in gene expression and methylation patterns. The ACTH-carcinoma showed alteration in N-Glycan biosynthesis, glycerophospholipid metabolism, purine and pyrimidine metabolism, whereas the silent corticotrope showed one carbon pool by folate, inositol phosphate metabolism, carbohydrate digestion and absorption and biosynthesis of unsaturated fatty acids. The GH-tumor showed alteration in pyruvate metabolism, propanoate metabolism, insulin secretion, and aldosterone synthesis and secretion. Our results suggest that there are several clones conforming a PT and some of them remain after surgical resection and can re-grow, this was confirmed by our scRNAseq analysis and immunofluorescence assays. We conclude that PT are genomically stable trough time, indicating that mechanisms other than somatic mutations are involved in pituitary tumorigenesis and that their biology could be driven by transcriptomically and epigenetically heterogeneous clones within the tumor itself.

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Acromegaly in the elderly: additional challenges in timely recognizing

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Background
Increased life expectancy and wider availability of neuroimaging lead to increase in diagnosis of acromegaly in elderly patients, after the age of 70. Delay in diagnosis is attributable to milder symptomatology, higher prevalence of comorbidities and symptoms overlapping with normal aging process.
Objective
To investigate clinical characteristics, presenting symptoms, comorbidities and treatment modalities of acromegaly in patients diagnosed after the age of 70.
Methods
Eleven patients with acromegaly diagnosed after the age of 70 (9 females, 81.8%) were identified from the group of 121 patients with pituitary adenoma (PA) diagnosed after the age of 70 (9.1%), in the PA Database ($n=1442$, 0.76%) of the Department of Neuroendocrinology for the past 18 years. Gender, age at diagnosis, tumor size, presenting signs and symptoms, presence of comorbidities and treatment modality were analyzed.

Results
Mean age at diagnosis was 73.5 ± 0.8 years (range: 70-78). All patients had two or more comorbidities (median 4). Six patients (54.5%) had microadenomas, two (18.2%) had mesoadenoma, while three (27.3%) had macroadenomas. Ten patients (90.9%) had typical acromegalic clinical symptoms and signs, while one male with the largest PA (3cm in diameter) presented with neurologic symptoms (headache, instability, vertigo). Arterial hypertension was diagnosed in nine patients (81.8%), cardiomyopathy and valvular heart disease in six (54.5%), diabetes and dyslipidemia in five (45.5%). One patient had breast cancer. One patient with pituitary macroadenoma had hypopituitarism and was replaced with hydrocortisone and levothyroxine. Baseline IGF-1 was 594.7 ± 65.7 ng/ml. Five patients (45.5%) underwent transsphenoidal surgery, without complications, with significant IGF-1 decrease (573.6 ± 148.4 ng/ml preoperatively vs 159.1 ± 45.2 ng/ml postoperatively). Six patients (54.5%) were medically treated with long-acting somatostatin analogues, with favorable therapeutic response after 19.5 ± 9.6 months of therapy (IGF-1 612.3 ± 31.6 ng/ml before vs. 168.5 ± 30.3 ng/ml upon treatment).
Conclusion
Recognition of acromegaly in the elderly may be challenging and delayed due to milder symptoms overlapping with aging and comorbidities. The prevalence of the elderly among newly diagnosed acromegaly patients is expected to expand. Further studies are needed to define optimal diagnostic and therapeutic management appropriate to patients advanced average age.

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Long-term Surgical Remission in Patients with Acromegaly in South-Eastern Norway

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Context
Immediate and sustained cure of acromegaly can only be achieved by surgery, however, most growth hormone (GH) producing adenomas are macroadenomas (≥ 10 mm) at diagnosis, with reported surgical cure rates of approximately 50% compared to microadenomas (<10 mm) with an expected higher cure rate (around 80%). Further, long-term data on remission rates after surgery are sparse.
Aim
Estimate short- and long-term surgical remission rates of patients with acromegaly and identify potentially predictive factors for long-term remission.
Methods
Patients who underwent surgery for a GH-producing pituitary adenoma between 2005-2020 were included from the local pituitary registry ($n=178$). Disease activity (GH and insulin-like growth factor 1, IGF-1), medical treatment, radiotherapy and reoperation were recorded at the short-term (one year postoperatively) and long-term (five year postoperatively) visit. Remission status was defined as IGF-1 ≤ 1.2 x upper limit of normal, without any additional surgical, radiation or pharmacological treatment for acromegaly. Baseline characteristics potentially predicting outcome (age, sex, GH and IGF-1 levels, tumor size (maximal diameter) and first treatment modality (preoperative with somatostatin analogues vs. direct surgery), were evaluated by multivariate regression models.
Results
Median age at diagnosis was 49 (IQR: 38-59) years, 46% were women. At diagnosis, 76% had macroadenomas and 24% microadenomas. Overall surgical remission rate at short-term was 54% and at long-term 41%. At short-term, 62% of patients with microadenomas and 52% with macroadenomas, obtained surgical remission. In patients who obtained persistent remission long-term, the remission rate was 58% for microadenomas and 37% for macroadenomas, with a trend towards higher remission rate in microadenomas ($P = 0.058$). In patients diagnosed in period 2005-2009, 2010-2013 and 2014-2020, the remission rates were 30%, 61% and 31%, respectively, at the long-term visit. Age, sex, GH and IGF-1 levels, tumor size and first treatment modality did not predict remission at long-term.
Conclusions
In unselected patients with acromegaly, the long-term remission rate after surgery was lower than expected and lower than the short-term outcomes. Our short-term outcomes are comparable to results of previous studies.

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Effects of acromegaly treatment on left ventricular systolic function assessed by speckle tracking echocardiography: results from a prospective single-center study

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Background
Despite the preserved left ventricular(LV) ejection fraction, patients with acromegaly are characterized by subclinical systolic dysfunction, i.e. abnormal global longitudinal strain(GLS) assessed by speckle-tracking echocardiography(STE). The effect of acromegaly treatment on LV systolic function assesed by STE has not been evaluated so far.
Patients and methods
Thirty two naïve acromegaly patients with no detectable heart disease were enrolled in a prospective, single-center study. 2D Echocardiography and STE GLS was performed at the diagnosis, 3 and 6 months on preoperative somatostatin receptor ligand(SRL) treatment and 3 months after the transsphenoidal surgery(TSS).
Results
Treatment with SRL resulted in a significant reduction in median GH& IGF-1 levels after 3 months from 9.1(3.2-21.9) ng/ml to 1.8(0.9-5.2) ng/ml($P<0.001$) and from 3.2(2.3-4.3)xULN to 1.5(1.1-2.5)xULN($P<0.001$), respectively. Longer SRL treatment did not lead to further decrease in GH& IGF-1 levels. Biochemical control on SRL was achieved in 25.8% and complete surgical remission was achieved in 41.7% of patients. TSS resulted in a decrease in IGF-1 compared to IGF-1 levels on SRL treatment: from 1.5(1.2-2.5)xULN to 1.3(1.0-1.6)xULN ($P=0.003$). Females had lower IGF-1 levels at baseline, on SRL and after TSS compared to males. The majority of patients had normal end diastolic and end systolic LV volumes(median LVEDV 56.4mL/m^2 in males and 44.5mL/m^2 in females, median LVESV 23.4mL/m^2 in males and 16.7mL/m^2 in females). Almost half of the patients(46.9%) had abnormal LVMi, however the median value of LVMi was normal in both sex groups: 99g/m^2 in males and 94g/m^2 in females. Most of the patients(78.1%) had abnormal LAVi and the median was 41.8mL/m^2. At baseline 50% of acromegaly patients had abnormal GLS, i.e. higher than -20% and the majority constituted men (62.5% vs. 37.5%). There was a positive correlation between baseline GLS and BMI $r=0.446$($P=0.011$) and BSA $r=0.411$($P=0.019$). GLS significantly improved after 3 months of SRL treatment compared to baseline: -20.4% vs. -20.0%($P=0.045$). There was no further change in GLS after 6 months of SRL therapy and no significant change after TSS. The median GLS was significantly lower in patients with surgical remission compared to those who had elevated GH& IGF-1 levels: -22.5% vs. -19.8%($P=0.029$). There was a positive correlation between GLS and IGF-1 levels after TSS $r=0.570$($P=0.007$).
Conclusions
The greatest beneficial effect of acromegaly treatment on LV systolic function is visible already after 3 months of preoperative SRL treatment, especially in women. Patients with surgical remission have better systolic function as assessed by STE compared to patients with persistent acromegaly.

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Clinicopathological aspects of growth-hormone and prolactin-producing pituitary neuroendocrine tumors

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Introduction
Pituitary neuroendocrine tumors (PitNET) are characterized by a heterogenous behavior. The immunohistochemical (IHC) staining of anterior pituitary hormones, along with that of pituitary transcription factors and with the clinical and biochemical characteristics of the patients can be integrated in a risk stratification system, which helps the therapeutic management.

Material and Methods
We analyzed 37 patients with confirmed diagnosis of acromegaly and 5 patients diagnosed with prolactinoma who underwent transsphenoidal pituitary surgery. The patient information was collected retrospectively. Using the postoperative tumour blocks, we performed morphological and IHC (anterior pituitary hormones: GH, PRL, TSH, FSH, LH, ACTH) analysis. Clinical data were extracted from medical charts. We correlated the IHC features of GH and PRL-secreting PAs with their clinical, laboratory and imaging data.
Results
Macroadenomas represented 88 % (37 cases) and the maximum mean diameter at diagnosis was 23,10 mm (the majority had Knosp grade II – 57%). Based on the morphological analysis (Hematoxylin and eosin method), histologically, the majority of tumors had diffuse growth pattern (80,95%). The intensity scores for anterior pituitary hormones were from 0 to 3+ (from absent to strong staining). We characterized the tumors according to the 2022 WHO classification. Immunohistochemistry showed 10 mixed mammosomatotroph PAs (GH/PRL) and 27 gonadotroph PAs. All of them showed intensive reaction for GH (3+). After surgery, only 2 patients were cured, 4 were in remission, 18 had controlled disease under medical treatment with somatostatin analogues and 10 under treatment with pegvisomant. Mean preoperative GH levels were 11.22 ng/ml (range: 0.97-44.7), and mean postoperative GH 4.82 ng/ml (range:0.09-30.5). Almost all patients diagnosed with prolactinomas (3 males and 1 female) had giant adenomas (maximum median tumour diameter was 43,6 mm), and after transsphenoidal surgery one patient was in clinical remission, 3 of them had controlled disease under treatment with dopaminergic agonists and one had uncontrolled disease under maximal doses.
Conclusions
The histopathological variability of pituitary adenomas (PAs) that cause growth hormone (GH) or prolactin (PRL) excess influences the clinical behavior, radiological characteristics and therapy response. The IHC classification and the radiological dimensions and extent influence disease control, and they are probably the best prognosis factors.
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Menin, p27 and pAKT role in prolactinoma development
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Molecular mechanisms involved in lactotrophs cell proliferation that led to prolactinoma development are not fully understood. Cyclin-dependant kinase (CDK) $p27^{Kip1}$ is a key cell cycle regulator, and it is regulated by Menin. The transgenic mice model *MEN1* $^{+/-}$, as the *p27* $^{-/-}$ knock-out mice, develop pituitary adenomas and other neuroendocrine tumours. Menin can also interfere with phosphorylated AKT (pAKT) function, known for its stimulatory action on cell proliferation. Additionally, PTEN is an inhibitor of AKT activation/phosphorylation. For better understanding, we studied these regulatory mechanisms in a mice model of prolactinoma that overexpress the human chorionic gonadotrophic hormone β-subunit (hCGβ), in which the transgenic female (hCGβ+), but not the transgenic male, develops lactotroph hyperplasia from 3-month of age onwards. We used 6 months old mice, and we analysed pituitary gene expression by Real-Time PCR and lactotroph protein expression by double indirect immunofluorescence detection (PRL+ protein+), comparing transgenic mice (hCGβ+) and wild-types (WT). We observed higher levels of *MEN1* gene expression in males vs females, without genotype differences. Male pituitaries presented similar levels of *p27* gene expression as WT females, without genotype differences. However, hCGβ+ females showed lower levels of *p27* compared to WTs. In addition, p27 protein expression was found to decrease in lactotrophs (PRL+) from hCGβ+ female pituitaries vs WTs. When Menin protein expression was analysed in female pituitaries, although no genotype differences were observed in the percentage of lactotrophs expressing Menin, important changes in its subcellular localization was observed: in lactotrophs from WT females Menin was expressed in cytoplasm and nuclei, while in hCGβ+ lactotrophs Menin was expressed mostly in cytoplasm. WT female lactotrophs showed low pAKT expression and it was most prevalent in cytoplasm while its expression was found increased in cytoplasm and nuclei in lactotrophs from hCGβ+ females. Additionally, lower levels of *PTEN* gene expression was observed in hCGβ+ pituitaries vs WTs. Pituitary *PTEN* gene expression was higher in males than females without genotype differences. We conclude that lower Menin expression in nulcei from hCGβ+ lactotrophs concomitant with lower *PTEN* expression could contribute to the decreased p27 and increased pAKT levels in transgenic females leading to tumour development. On the other hand, the higher levels of pituitary *MEN1* and *PTEN* observed in males could help to control the cell proliferation rate in this sex.
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Morphological and functional parameters of the cardiovascular system in acromegalic patients: impact of body composition
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Objective
Cardiovascular diseases are the most common comorbidities in acromegaly. Potential parameters in pathology of cardiovascular comorbidities are changes in levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) as well as body composition parameters.
Purpose
The aim of this study was to examine morphological and functional parameters of the cardiovascular system by echocardiography and to assess its relationship with disease activity and body composition parameters.
Methods
We prospectively enrolled 129 acromegalic patients (82 females, 47 males) and 80 healthy controls (53 females, 27 males) matched for age, gender, and BMI. All patients underwent two-dimensional echocardiography. Body composition parameters were assessed by dual-energy X-ray absorptiometry.
Results
Acromegaly patients presented with higher left ventricle mass (LVM) compared to controls (LVMI: 123 $\pm$ 45 g/m^2 vs 83 $\pm$ 16 g/m^2, $P<0.001$). Prevalence of left ventricle hypertrophy in acromegaly patients was 67% (78% concentric, 22% eccentric). IGF -1 levels, BMI, and lean mass positively correlated with LVM in all acromegaly patients ($P<0.001$). Fat mass positively correlated with LVM in females ($r=0.306$, $P=0.005$), but this correlation was not found in males. We did not find any difference in size of the left and right ventricle between acromegaly patients and controls. Acromegaly patients presented with left atrium enlargement, diastolic dysfunction and low incidence of systolic dysfunction. Valvopathy was found in 43% of patients with predominant (31%) prevalence of mitral regurgitation.
Conclusions
Our study demonstrates higher prevalence of cardiovascular comorbidities in acromegaly patients and the impact of IGF-1 levels and body composition parameters in pathology in some of these comorbidities.
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Design of the foresiGHt Trial: A Multicenter, Randomized, Placebo- and Active-Controlled Trial to Compare Once-Weekly Lonapegsomatropin to Placebo and Daily Somatropin in Adults with Growth Hormone Deficiency (GHD)
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Background
Adult GHD results from insufficient growth hormone (GH) secretion from the anterior pituitary gland and may represent either a continuation of childhood-onset GHD or GHD acquired during adulthood. Clinically, adult GHD is associated with central adiposity, decreased lean muscle mass, increased fat mass,

decreased bone mineral density, and reduced quality of life. Current standard of care consists of GH replacement via daily injections. Lonapegsomatropin (SKYTROFA; TransCon hGH), a once-weekly prodrug of somatropin approved for the treatment of pediatric GHD by the FDA and EMA, uses TransCon technology to transiently link a parent drug to an inert carrier and achieve sustained release of active, unmodified somatropin under physiologic conditions. The safety and efficacy of lonapegsomatropin have previously been evaluated in three phase 3 trials in pediatric GHD. Change in body composition in both pediatric and adult GHD reflects biologic activity of GH and clinical efficacy of GH replacement.
Methods
The primary objective of the foresiGHt trial is to evaluate the efficacy of once-weekly lonapegsomatropin compared to placebo at 38 weeks in adults with GHD. The trial has been conducted at approximately 120 sites in North America, Europe, Asia, and Oceania. Approximately 240 subjects have been randomized 1:1:1 to once-weekly lonapegsomatropin, once-weekly placebo, or daily somatropin. Subjects will be treatment-naïve or without GH therapy for at least 12 months. Subjects with well-controlled non-insulin dependent diabetes mellitus (HbA1c $\leq$ 7.5%) will be eligible. Following screening, the 38-week treatment period will consist of a 12-week gradual dose titration period and 26 weeks of fixed dose maintenance. Fixed dosing will be used to ensure maximal comparability across the treatment arms in the trial. Three dosing groups per arm will be established to allow for differences in age and oral estrogen intake in women. The primary endpoint is change from baseline in trunk percent fat at week 38, as measured by dual energy X-ray absorptiometry (DXA). Secondary efficacy endpoints are change from baseline in trunk fat mass and change in total body lean mass at week 38. Exploratory efficacy endpoints include total body fat mass, trunk lean mass, visceral adipose tissue, and patient-reported outcomes.
Conclusion
The ongoing global Phase 3 foresiGHt trial is designed to assess the efficacy, safety, and tolerability of lonapegsomatropin by weekly administration, compared to weekly placebo and daily hGH replacement therapy in adults with GHD.

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Lanreotide-Induced Acalculous Acute Pancreatitis in a Person with Acromegaly: an Unexpected Severe Side Effect

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Introduction
Somatostatin analogues (SA) are the first-line treatment for Acromegaly in patients whose surgery failed to achieve cure or it was contraindicated. The main reported adverse events of SA are mild and transient, and include nausea, abdominal cramps, diarrhea and flatulence. Other side effects are of rare occurrence.
Case report
The authors describe a case of a 44-year-old previously asymptomatic male patient with a growth hormone-secreting pituitary macroadenoma partially involving the left cavernous sinus who was submitted to debulking transsphenoidal surgery. Biochemical and imaging remission were not accomplished and adjuvant treatment was initiated with lanreotide 120 mg every 8 weeks. Three days after the first administration, the patient attended the Emergency Department complaining of general abdominal pain, along with fever *that resolved with* paracetamol, nausea and acholia. He denied choluria, jaundice and alcohol intake. Physical examination revealed a slight *right flank tenderness.* Biochemical analysis exhibited high C-reactive protein (10.69 [0-0.5] mg/dl) and high serum pancreatic amylase (178 [13-53] U/l) and lipase (259 [13-60] U/l) levels. The remaining analytical investigation was unremarkable. A transabdominal ultrasonography showed no lithiasis, a *non-dilated biliary* tract and a normal gallbladder. Acalculous acute pancreatitis was assumed, but the patient refused hospitalization for proper treatment and investigation. Therefore, he was actively monitored in the outpatient setting. He got hydrated, progressively reintroduced the diet and avoided alcohol intake, with clinical improvement after one week. One month later, serum pancreatic amylase (145 [13-53] U/l) and lipase (245 [13-60] U/l) levels persisted high, but C-reactive protein level dropped (0.13 [0-0.5] mg/dl) and transabdominal ultrasound remained unremarkable. Two months after the episode, C-reactive protein (0.05 [0-0.5] mg/dl) level persisted low, and serum pancreatic amylase (67 [13-53] U/l) and lipase (102 [13-53] U/l) levels dropped near to the upper normal limit, with no clinical relapse. Acalculous acute pancreatitis was assumed, and lanreotide was presumed as the culprit.
Conclusions
As far as the authors know, the association between acalculous acute pancreatitis and a SA was only reported once in the literature. This may be due to spasm of the sphincter of Oddi with subsequent biliary-pancreatic obstruction. This case report highlights the need to raise awareness on SA-induced acute pancreatitis and include it in the differential diagnosis of a patient who present abdominal complaints after initiating a treatment with a SA.

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P434

Awaken a sleeping giant: Incidentally discovered pituitary gigantism

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Introduction
Pituitary gigantism is a rare disorder characterized by growth hormone (GH) excess that occurs before epiphyseal growth plates fusion leading to rapid and excessive linear growth in childhood and very tall adult stature. It can be sporadic or coexist with genetic disorders such as FIPA, X-LAG, McCune-Albright, Carney complex, MEN 1 or 4, and Neurofibromatosis type 1.
Case report
We present a case of a 12 years old boy with no medical history, who presented in our clinic with pituitary incidentaloma detected on head CT scan for craniocerebral injury due to falling from the same level. The patient complained of intermittent headaches for about three years, tall stature, and large hands and feet (the mother reported an increase in the size of his shoes from 35 to 43). On physical examination, his height was 173.5 cm (+ 3 DS), with proportionate growth, height velocity approximately 10 cm in 10 months (reported by his mother), predictive target height 195 cm, parenteral target height 179 cm, body weight 52 kg (+ 1.13 DS), Tanner stage II. Laboratory tests showed elevated levels of serum age-adjusted and sex-adjusted IGF-1 (647 ng/ml, NV: 49-487 ng/ml) and failure of GH suppression during an oral glucose tolerance test (nadir GH 35 ng/ml). The other pituitary hormones were within normal limits. Bone age was normal for chronological age. MRI of the sellar region showed pituitary macroadenoma with dimensions of 23/19/11 mm with bilateral extension but no cavernous sinus invasion or optic chiasm involvement. Visual field evaluation was normal. He underwent transsphenoidal surgery and the histopathology report revealed positive immunohistochemistry for GH and prolactin, high Ki67 (25%) and positive p53. Three months after surgery, IGF-1 level normalized (390 ng/ml, NV: 49-487 ng/ml), GH secretion decreased significantly, but without suppression on OGTT (nadir GH 2.57 ng/ml), and no residual tumor was detected on MRI. There was no hypopituitarism after surgery. Treatment with first generation somatostatin analogues was initiated without response. In the absence of disease control, Pegvisomant was prescribed with favorable outcomes (IGF-1 = 160 ng/ml and growth stagnation), but after three months of treatment the patient presented elevated liver enzymes. The treatment with Pegvisomant was stopped and Pasireotide was initiated.
Conclusions
Pituitary gigantism is a rare disease, caused by a growth hormone secreting pituitary adenoma. Management of the disease represents a real challenge due to the lack of experience in children. Close follow-up is mandatory to prevent complications and improve survival rates.

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P435

Osilodrostat as an effective and safe treatment for ectopic Cushing Syndrome- case report

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Osilodrostat as an inhibitor of adrenal 11B-hydroxylas, is an effective medication used in the management of endogenous hypercortisolism. There are limited data regarding usage of osilodrostat in ectopic Cushing Syndrome (CS). Surgery is usually the first line treatment in ectopic CS, however the source of ectopic hormonal production often remains undiscovered for a long period of time. Meanwhile dangerous state of severe hypercortisolism needs to be managed pharmacologically by steroidogenesis inhibitors. We present a case of a 72 year- old male patient with diabetes mellitus, hypertension, obesity, dyslipidemia who was admitted to Emergency Department due to Transient Ischemic attack (TIA), severe hypokalemia and hyperglycemia.

Physically patient presented Cushing Syndrome's features. Additional biochemical assesment showed ACTH dependent hypercortisolemia (ACTH 197 pg/ml, Cortisol 76 ug/dl). Patient was transferred to Endocrinology Department. Hormonal tests suggested ectopic Cushing Syndrome. Either 2-[18F]FDG PET/CT or [68Ga]Ga-DOTA-TATE PET/CT didn't show potential ectopic lesion. Pituitary MRI showed Rathe cyst. We put the patient on metyrapone (up to 2250 mg) and observed dropping of cortisol level. After 3 months of treatment metyrapone was withdrawn and osilodrostat was started 1mg BID, followed by dose reduction to 1mg per day. The Patient reached satisfactory clinical and biochemical control of Cushing Syndrome. Since cortisol levels dropped, we plan repetition of [68Ga]Ga-DOTA-TATE PET/CT. To sum up, osilodrostat seems to be an effective, safe and convenient treatment in management of severe hypercortisolism in patients with ectopic CS.

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P436

The Indian Male Aging Study Shows Differential Relationships Between Age and Modifiable Risk Factors for Hypothalamic-Pituitary-Testicular Axis Disruptions in Older Men

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Introduction
It is unknown what causes ageing men to have lower testosterone levels and how those levels relate to risk factors. Less research has been done on the health of ageing males than on postmenopausal women.
Objective
The aim was to look into how men-aging lifestyles and health related to their levels of reproductive hormones.
Method
A prospective cohort study in Indian men included 320 community-dwelling men between the ages of 41 and 78 for this baseline cross-sectional survey. Equal numbers of men were chosen from the general population to represent each of the four age groups: 41-48, 51-58, 61-68, and 71-78 year. As long as the person could respond to the mail invitation and give written informed consent, there were no particular exclusion criteria. As soon as the null hypothesis could be rejected at the 0.04 (two-tailed) level, the results were deemed statistically significant. SAS proc mixed and STATA version 9.2 were used for all data analyses.
Results
Different forms of changed function were linked to four predictors, including: 1) Older age: decreased free T (FT; 3.11 pmol/liter/yr, $P<0.002$) and elevated LH, suggesting the reduced testicular function, 2) Obesity: lower total T (TT; 2.31 nmol/liter) and FT (17.61 pmol/liter) for body mass index (BMI; 24 to 29 kg/m2); lower TT (5.08 nmol/liter) and FT (52.71 pmol/liter) for BMI 29 kg/m2 or above ($P<0.002$-0.02, referent: BMI 24 kg/m2); 3) comorbidity: greater LH in older men but unchanged TT (0.81 nmol/liter, $P<0.02$) in younger men; 4. Smoking: higher SHBG (5.95 nmol/liter, $P<0.002$) and LH (0.76 U/liter, $P<0.02$) with increased TT (1.30 nmol/liter, $P<0.002$) but not FT, consistent with a resetting of T-LH-negative feedback due to raised SHBG.
Conclusions
Age-related testicular dysfunction is accompanied by complex multiple abnormalities in the hypothalamic-pituitary-testicular axis function in ageing men. Varied risk variables have different relationships with these changes. Some risk factors contribute to the T decrease independently of age, whereas others interact with it. These possibly modifiable risk variables point to potential preventive steps that men can take to preserve T as they age.

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P437

Acromegaly management in the Scandinavian countries – a DELPHI consensus survey

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Background
Acromegaly is associated with increased morbidity and mortality if left untreated. The therapeutic options include surgery, medical treatment, and radiotherapy. Guidelines regarding treatment algorithms and follow-up vary considerably.
Aim
To evaluate consensus on the treatment and follow-up of acromegaly in the Scandinavian countries.
Methods
To map the landscape of acromegaly management in the Scandinavian countries, a Delphi process was used. An expert panel developed 37 statements on the treatment and follow-up of acromegaly. Dedicated endocrinologists ($n=35$) from the Scandinavian countries were invited to participate in three Delphi rounds and rate their extent of agreement with statements concerning management of acromegaly, using a Likert-type scale (1-7). Consensus was defined as $\geq$ 80% of panelists rating their agreement as 5–7 on the Likert-type scale.
Results
33 endocrinologists (94 %) answered the survey (55 % women; mean 19 years of experience). Consensus was achieved for 16 (43%) statements distributed as follows: *Primary treatment* 2/4 (50%), *preoperative treatment with Somatostatin analogues* 0/4 (0%), *second- and third-line treatment* 7/19 (36%), *treatment in relation to pregnancy* 5/7 (71%), *long-term follow-up after disease control* 2/4 (50%).
Conclusion
This work reflects the clinical perspective of expert endocrinologist from the Scandinavian countries. In >50 % of the statements, consensus was not reached, which may reflect the complexity of the disease and its management, and/or a shortage of evidence-based data.

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The Role of the GH Receptor Polymorphism as Prognostic Factor of Vertebral Fractures in Acromegaly Patients Resistant to First Generation SSAs and Treated with GH Receptor Antagonist or Second-Generation Somatostatin Ligand

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Acromegaly is associated with skeletal fragility and an increased prevalence of vertebral fractures (VF). In recent years several authors have tried to investigate the markers that can predict the risk of bone fragility in this endocrine disorder. Two different isoforms of the GH receptor (GHR) have been described so far, which differ in the presence or absence of a transcript of exon 3 of the GHR gene. Both isoforms produce a functional receptor, but the exon 3-deleted isoforms (d3-GHR) have greater sensitivity to endogenous and recombinant GH than the full-length isoform (fl-GHR). We conducted a longitudinal, retrospective, observational, single-center study of first-generation SSA-resistant acromegaly patients, with the aim of investigating the role of GHR polymorphism as a prognostic factor of incidental VF (I-VF) in first-generation SSA-resistant acromegalic patients and treated with GH receptor antagonist (Pegvisomant) or second-generation somatostatin ligand (Pasireotide Lar). 72 patients with acromegaly were included. 28 patients carried d3-GHR isoform (38.9%) and 44 patients carried fl-GHR isoform (61.1%). At baseline, all patients were affected by active acromegaly; 46 patients were treated with Pegvisomant in combination with first generation SSA and 26 were treated with Pasireotide Lar. 18 patients (25%) carried P-VFs. At last follow-up, 58 patients achieved biochemical control of acromegaly (80.6%). 14 patients experienced the occurrence of I-VFs. From the group

treated with Pegvisomant in combination with first generation SSA, 32 patients carried fl-GHR polymorphism and 14 carried d3-GHR polymorphism. At baseline, 10 patients (21.7%) were I-VF carriers. At follow-up, 8 patients developed P-VF (17.4%). I-VF occurred more frequently in patients carrying fl-GHR isoform compared to d3-GHR ($P=0.04$). From the group treated with Pasireotide Lar, 12 patients carried fl-GHR isoform and 14 patients carried d3-GHR isoform. At baseline, 8 patients (30.8%) were I-VF carriers. At follow-up, 6 patients developed P-VF (23.1%). I-VF occurred more frequently in patients carrying d3-GHR isoform than fl-GHR ($P=0.01$) and in patients with P-VF as compared to patients without P-VF ($P=0.05$). In conclusion, the GH receptor polymorphism could assume greater relevance as a prognostic factor of VF in acromegaly patients. In the future, the knowledge of the GHR polymorphism may improve the therapeutic approach of acromegaly patients, tailored to the individual patient, in the context of personalized medicine.

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P439

Serial sampling of dried blood spots collected by a novel automated body-worn system, Fluispotter®

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Repeated blood sampling is required in certain clinical and research settings, which is currently performed by drawing blood from venous catheters requiring manual handling of each sample at time of collection. A novel body-worn device for repeated serial samples, Fluispotter®, with automated extraction, collection and storage of up to 20 venous dried blood spot samples (DBS) over the course of 20 h may overcome problems with current methods for serial sampling. The purpose of this study was to assess the performance and safety of Fluispotter for the first time in healthy subjects. Fluispotter consists of a cartridge with tubing, reservoir for flushing solution, pumps and filter-paper and a multi-lumen catheter placed in the brachial vein. The volumetric DBS technology used in the Fluispotter has previously been tested *ex vivo* for cortisol assessment by comparing cortisol concentrations from dried blood spots with cortisol plasma samples[1]. The interassay accuracy and precision were less than 10% across a range of different haematocrit values. The plasma cortisol concentration was predicted from cortisol concentration measurements extracted from the DBS using the following formula:

$$PC\_plasma = C\_(DBS)/((0.92+(-0.876 \times HCT)))$$

We recruited healthy subjects for testing in an in-hospital setting. Fluispotter was attached to 22 healthy subjects of which 9/22 (40.9 %) participants had all 20 samples taken successfully, which was lower than the expected 80% ($P=0.02$). The main reason for sample failure was clogging of blood flow which was observed in 11/22 (50 %) of the participants. No serious adverse events occurred, and the participants rated the pain from insertion and removal of catheter as very low. A cortisol profile showed nadir values at midnight and highest values at 5 a.m. In conclusion, although full sampling was not successful in all participants, the Fluispotter technology proved safe and highly acceptable to the participants. The blood clogging was expected to be solvable by simple technical amendments. Producing the expected cortisol profile without the requirement of staff during sample collection provides promising future applications for studying circadian variations of different compounds in the circulation.

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1. Adhikari *et al*. Fluispotter, a novel automated and wearable device for accurate volume serial dried blood spot sampling. Bioanalysis. Methodology. Vol. 12:10; p.665-681

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P440

DUONEN multicenter study - personalized PRRT treatment with 177Lu- or 177Lu/90Y-DOTA-TATE in patients with neuroendocrine tumors based on individual dosimetry

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Introduction
The good expression of somatostatin receptors in neuroendocrine tumor tissue enables effective treatment with peptide receptor radionuclide therapy (PRRT). To date, there is no clear consensus on the optimal PRRT arrangement due to the possibility of the use of different radiopharmaceutical regimens. In theory, the simultaneous use of two radionuclides (90Y and 177Lu) with different energy and radiation ranges should be more effective than monotherapy. The main objectives of DUONEN (a phase III study, EUDRACT No: 2020-006068-99) are: - development of a personalized (dosimetry-based) PRRT algorithm for patients with disseminated NETs -evaluation of the safety and effectiveness of personalized therapy with mixture of [177Lu]Lu- and [90Y] Y-DOTATATE compared to the use of [177Lu]Lu-DOTATATE in standard doses (7400MBq)
Methods
92 adult patients with advanced, unresectable well-differentiated (G1/G2) NETs, progressing on long-acting SSA are randomized into four arms: - A: treated with [177Lu]Lu -DOTATATE with constant radioactivity of 7400MBq per cycle - B: treated with a mixture of [177Lu]Lu-DOTATATE and [90Y]Y-DOTATATE, initially in a ratio of 3700:1850MBq/MBq, with constant [177Lu]Lu -DOTATATE dose in all cycles, [90Y]Y-DOTATATE dose is adjusted in each cycle based on bone marrow and kidney dosimetry to maintain the highest possible radiation dose in tumor tissue - C: treated with a mixture of [177Lu]Lu-DOTATATE and [90Y]Y-DOTATATE, initially in a ratio of 3700:1850 MBq/MBq, analogously to arm B, except that the dose of [90Y] Yu-DOTATATE is constant and the dose of [177Lu]Lu-DOTATATE will depend on the dosimetry results - D: treated with [177Lu] Lu -DOTATATE initially with a dose of 7400MBq and then with doses based on individual dosimetry results The treatment efficacy will be evaluated on morphological imaging (TK or MR) according to RECIST 1.1 criteria and compared between arms. The safety of individual PRRT schemes will be assessed by biochemical follow-up of the kidney and bone marrow.
Results
11 patients have already started PRRT (arm A-3, B-4, C-1, D-3 cases). Total reported cycles given 25, including 14 fixed doses (firsts doses or arm A). In 8 of 11 cycles provided for adjustment, the dose of radiopharmaceutical estimated on the basis of personalized dosimetry was increased in 6 and decreased in 2 cases.
Conclusion
Personalized renal and bone marrow dosimetry influences PRRT doses in subsequent treatment cycles, which is likely to affect the results and safety of therapy.
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P441

Prevalence and related risk factors of simple renal cysts and nephrolithiasis in acromegaly

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Background
The growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis has effects on renal growth and electrolyte regulation. However, data on adverse renal

comorbidities such as renal cysts and stones in acromegaly is scarce. The current study aimed to investigate the prevalence of radiologically detectable renal comorbidities and possible related factors in the acromegaly population.
Methods
A total of 125 patients with acromegaly (46.4 ± 11.6 years, 68 females/57 males) and 114 age-sex matched healthy subjects (45.3 ± 12.4 years, 59 females/55 males) were included in the study retrospectively. Abdominal/urinary system ultrasonography or abdominal computed tomography results at the time of diagnosis in patients with acromegaly and at any time in healthy controls were examined. Demographic data, clinical history, and laboratory data of the patients were also recorded.
Results
Renal cyst prevalence (28.8% vs. 8.8%, $P<0.001$) and the longitudinal and transverse lengths of kidneys ($P<0.05$) were significantly higher in patients with acromegaly compared to the control group. There was no significant difference between the two groups in terms of the number of renal cysts. The presence of acromegaly disease increased the risk of renal cyst formation 12.8 fold (95% confidence interval, 2.8-58.2, $P=0.01$). The frequency of nephrolithiasis in acromegaly patients was similar to the control group (15.2% vs. 7.9%, $P=0.08$). Patients with acromegaly with renal cysts ($n=36$) compared to the group without cysts ($n=89$) were older (53.9 ± 10.0 vs. 43.3 ± 10.8 years, $P<0.001$), had a higher male sex frequency (69.4% vs. 35.9%, $P=0.001$), had a longer pre-diagnosis symptom duration (5 (interquartile range, 4-10) vs. 4 (2-5) years, $P=0.005$), and had a higher active smoking frequency (54.3% vs. 33.8%, $P=0.04$) and incidence of hypertension (54.3% vs. 31.8%, $P=0.02$) and diabetes mellitus (47.2% vs. 23.6%, $P=0.01$) at the time of diagnosis. Multivariate logistic regression analysis showed that age was an independent risk factor associated with the presence of renal cysts in patients with acromegaly. There was no statistically significant difference between acromegaly patients with and without cysts in terms of basal GH, nadir GH levels during oral glucose tolerance test, IGF-1xupper limit normal levels, kidney lengths, presence of kidney stones, estimated glomerular filtration rates, and serum electrolyte levels.
Conclusions
The present study showed that acromegaly disease significantly increased the prevalence of renal cysts and kidney lengths compared to the age- and sex-matched healthy population, while the prevalence of nephrolithiasis was similar. Advanced age was found to be an independent risk factor for renal cyst formation in patients with acromegaly.

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Phosphoproteomics analysis of aryl hydrocarbon receptor interacting protein (AIP) knockout cells reveals AIP-mediated kinase signalling cascades

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Introduction
Aryl hydrocarbon receptor interacting protein (AIP) is a multifunctional co-chaperone protein: it behaves as a tumour suppressor in the pituitary, but may have other roles including oncogenic function in other tissues. Protein phosphorylation is an important posttranslational modification that regulates protein activity, which is crucial for understanding protein function. To understand the molecular pathways altered in AIP deficient cells, we have performed global phosphoproteomics analysis of Aip-knockout mouse embryonic fibroblasts (Aip-KO MEFs) cells.
Aim
The aim of this study was to discover altered protein phosphorylation-related signalling pathways in Aip-KO MEFs.
Method
Phosphoproteomics analysis was performed by mass spectrometry (MS). Lysates were collected in four replicates from WT and Aip-KO cells. Phosphopeptides were enriched using titanium dioxide and subsequently analysed by LC-MS/MS. Ingenuity pathway analysis (IPA) was used for pathway analysis.
Results
We have identified 352 significantly altered phosphopeptides (200 hyper- and 152-hypophosphorylated) in Aip-KO MEFs compared to wild type cells. Among the hyperphosphorylated peptides, 10 were kinases and five were phosphatases. IPA analysis revealed two significantly activated pathways. The "Endocannabinoid cancer inhibition pathway' (Camkk2, Map2k7, Prkab2, Smpd3, Tcf4 and Twist1) was not previously suggested to be involved with AIP. The "Epithelial adherens junction signalling' (Arhgef17, Ctnna1, Nectin-1, Prkab2, Tcf4, and Vcl) pathway we have previously identified in gene expression and protein data of AIPpos human and mouse pituitary tumours. Functional enrichment analysis showed adherens junction, tight junction and actin cytoskeleton are the top significantly enriched pathways. Protein-protein interaction networks also showed the tight junction and signalling by Rho GTPases. Multiple kinase-mediated signalling pathways are altered in Aip-KO MEFs. The exact mechanism for the differential phosphorylation for these kinases needs to be validated by functional assays and explored further.
Conclusions
This study revealed novel insights into AIP-mediated signalling events and can be used as a valuable resource for further understanding of its function in invasive pituitary tumour development. It appears that adherens junction and tight junction pathways are of the most enriched pathways de-regulated in Aip-KO MEFs, suggesting a critical role of AIP in these pathways. Therefore, new treatments targeting these pathways may have potential to the management of patients with aggressive *AIP*pos pituitary tumours.

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Pooled analysis of osilodrostat dosing across LINC 2, LINC 3 and LINC 4 in Cushing's disease

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Introduction
Phase II (LINC2, NCT01331239) and Phase III (LINC3, NCT02180217; LINC4, NCT02697734) studies showed that osilodrostat, a potent oral 11β-hydroxylase inhibitor, was an effective long-term treatment for Cushing's disease patients. In this LINC programme pooled analysis, we examined how dose uptitration and adjustments during long-term maintenance can provide rapid, sustained mean urinary free cortisol (mUFC) control, and minimise AEs.
Methods
Data from 229 patients enrolled in LINC2, LINC3 (both mUFC>1.5x the upper limit of normal [ULN]) and LINC4 (mUFC>1.3xULN) were pooled and analysed. Placebo treatment periods were excluded. In LINC2, patients started open-label osilodrostat 2 mg twice daily (bid), with dose increases every 2 weeks (W) if mUFC>ULN. In LINC3, patients started open-label osilodrostat 2 mg bid, with dose increases every 2W until W12 if mUFC>ULN, then every 4W thereafter. In LINC4, patients were randomised to osilodrostat 2 mg bid or placebo (W1–W12), then increased every 3W until W12 if mUFC>ULN and every 3W thereafter. Maximum dose was 30 mg bid in all studies (reduced from 50 mg bid in LINC2 core phase). Dose adjustments were permitted during the extensions based on efficacy/tolerability.
Results
Median (min–max) osilodrostat exposure was 100W (1–351). Median (min–max) dose was 6.8 mg/day (1–47); dose needed to achieve mUFC control varied widely. Median time to first mUFC control: all patients, 35 days (D; 95% confidence interval [CI]:34–41); by baseline mUFC severity: <2xULN, 28D (95% CI:17–34); 2–5xULN, 40D (95% CI:34–42); >5xULN, 52D (95% CI:41–56). Median time to first AE of special interest (AESI) was 12W (95% CI:10–15); AESIs occurred at different osilodrostat doses. Fewer hypocortisolism-related (baseline to W12, 23%; W12–48, 24%; W48–72, 8%; W72–≤ W351, 20%) and adrenal hormone precursor accumulation-related AEs (baseline to W12, 36%; W12–48, 37%; W48–72, 14%; W72–≤ W351, 18%) occurred during long-term maintenance than dose titration. AESIs were mostly manageable with dose interruption and/or additional therapy, with few patients discontinuing treatment (hypocortisolism-related [$n=8$]; adrenal hormone precursor accumulation-related [$n=3$]).

Conclusions
Osilodrostat provided sustained mUFC control in all studies; time to control was shorter with lower baseline mUFC values. Median daily osilodrostat dose was low but varied widely. Dose titration differed between studies, but AESIs were less frequent during long-term treatment than dose uptitration and were mostly manageable without stopping treatment. Personalised therapy during dose titration and lifelong monitoring are needed to optimise clinical outcomes.

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Sleep Quality and Associated Factors in Patients with Non-functioning Pituitary Adenoma

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Aim
Sleep disturbances are widespread and closely associated with pituitary diseases, even those under long-term therapeutic management. The aim of this study was to investigate sleep quality, depression, anxiety, and physical activity in patients with non-functioning pituitary adenoma (NFPA) and determine the factors that might be associated with decreased quality of sleep.
Method
Eighty-two patients with NFPAs and 82 age- and gender-matched control subjects were included. Information on the patients' clinical findings, laboratories and imagings, therapies for pituitary insufficiency were documented. Pittsburgh Sleep Quality Index (PSQI), Hospital Anxiety and Depression Scale (HADS) and International Physical Activity Questionnaire (IPAQ-SF) were used to evaluate sleep quality, depression, anxiety, and physical activity of participants.
Results
Eighty-six percent of the patients with NFPAs had macroadenoma and mean largest diameter was 22.0 mm. Intact pituitary function was present in 47.6% of patients with NFPAs. In the NFPA group, 57.3% of patients had decreased sleep quality, while 35.4% of patients in the control group ($P=0.005$). Anxiety and depression scores were higher and physical activity scores were lower in NFPAs than in the control group ($P<0.05$). Although there was no relationship between the presence of hydrocortisone replacement or total daily dosage and sleep quality in patients with secondary adrenal insufficiency ($P>0.05$), there was a strong positive correlation between PSQI and morning hydrocortisone replacement time ($r=0.834$, $P<0.001$). The presence of both transcranial surgery and diabetes insipidus was also found to be significantly higher in the group with decreased sleep quality ($P<0.05$). There was a negative correlation between PSQI and IGF-1 and free T4 levels in patients with NFPAs ($r=$-0.259, $P=0.01$) ($r=$-0.392, $P<0.01$). A multivariate logistic regression model revealed that depression score and free T4 level in the upper half of the normal limit were the most associated factors for sleep quality.
Conclusions
Our study indicated that patients with NFPAs had decreased sleep quality compared to age- and gender- matched controls. Presence of depression and a free T4 level in the upper half of the normal range were the most associated factors, along with presence of transcranial surgery, low IGF-1 levels, diabetes insipidus, and morning hydrocortisone replacement time.

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Psychopathological characteristics in patients with arginine vasopressin deficiency (central diabetes insipidus) and primary polydipsia

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Introduction
The differential diagnosis between arginine vasopressin deficiency (AVP-D), formally known as central diabetes insipidus, and primary polydipsia (PP) is challenging. In clinical routine, psychopathologic findings are often used as a hallmark for diagnosing PP; thus, it is often referred to as psychogenic polydipsia. Yet, psychopathologic characteristics are barely assessed in patients with AVP-D, and to date, no data exist comparing AVP-D and PP with regard to these features. Therefore, in this study, we aimed to compare levels of anxiety, depression, alexithymia, and overall mental health in patients with AVP-D and PP.
Methods
This study combined data from two diagnostic studies conducted at three tertiary medical centers. In total, 82 participants ($n=39$ with AVP-D, $n=28$ with PP, and $n=15$ healthy controls [HC]) underwent a psychological evaluation with standardized questionnaires at study inclusion. Anxiety levels were assessed using the State-Trait Anxiety Inventory, mood using the Beck's Depression Inventory, alexithymia using the Toronto Alexithymia Scale, and overall physical and mental health using the Short Form 36 Health Survey (SF-36). Higher STAI, BDI, and TAS scores indicate higher anxiety, depression, and alexithymia levels. Higher SF-36 scores indicate better health and less disability.
Results
Compared with HC, patients with AVP-D and PP showed increased levels of anxiety (HC 28 points [24, 31] vs. AVP-D 36 points [31, 45], $P<0.01$; vs. PP 38 points [33, 46], $P<0.01$), depression (HC one point [0, 2] vs. AVP-D 7 points [4, 14], $P<0.01$; vs. PP 7 points [3, 13], $P<0.01$), and alexithymia (HC 30 points [29, 37] vs. AVP-D 43 points [35, 54], $P<0.01$; vs. PP 46 points [37, 55], $P<0.01$). Levels of anxiety, depression, and alexithymia showed no difference between patients with AVP-D and PP ($P=0.58$, $P=0.90$, $P=0.50$). Compared with HC, patients with AVP-D and PP reported comparable reduced self-reported mental health scores (HC 84 [68, 88] vs. AVP-D 60 [52, 80], $P=0.05$; vs PP 60 [47, 74], $P<0.01$).
Conclusion
This is the first study demonstrating comparable increased levels of anxiety, depression, alexithymia, and overall reduced mental health in patients with AVP-D and PP. Based on these data, psychopathological findings should not be used as a hallmark to differentiate between both conditions.

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Hyperosmolar Hyperglycaemic State (HHS) and severe decompensated heart failure as presenting features of ectopic ACTH Syndrome

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Ectopic ACTH syndrome is a rare condition occurring in five to ten percent of ACTH dependent hypercortisolism. We present the case of a fifty eight year old gentleman who presented with severe hyperosmolar hyperglycaemic state (blood glucose fifty seven mmol/l) and acute decompensated heart failure associated with elevated liver enzymes. Liver ultrasound followed by computed tomography of thorax abdomen and pelvis showed a lung tumour with liver metastases. Clinical suspicion of Cushing's syndrome was confirmed by with an overnight dexamethasone suppression cortisol of three thousand nine hundred and forty two nmol/l. A twenty four hour urine free cortisol was markedly elevated at a hundred fold with an adrenocorticotropin hormone level of one thousand four hundred and forty six pg/ml (7.2-63.3). Liver biopsy confirmed small cell carcinoma. Following initial treatment of his hyperosmolar hyperglycaemic state and heart failure, he was commenced on four grams of metyrapone per day which normalised his cortisol day curve. His insulin therapy and diuretics were later stopped and he maintained euglycaemia without glucose lowering therapy. Following carboplatin/etoposide chemotherapy, his metyrapone dose was reduced to two grams/day due to hypocortislaemia and replacement Hydrocortisone was added. This is a case of very severe hypercortisolaemia secondary to ectopic ACTH syndrome presenting with life threatening complications. Prompt diagnosis and rapid cortisol control with high dose metyrapone resulted in marked clinical and biochemical improvement.

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The diagnostic accuracy of dex-CRH test in differentiating between Cushing's disease and pseudo-Cushing syndrome. A single-center experience

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Background
Distinguishing pseudo-Cushing syndrome (PCS) from mild forms of Cushing's disease (CD) is a challenge. The dexamethasone-Corticotropin Releasing Hormone test (dex-CRH) assumes that cortisol response to CRH is preserved in CD while suppressed in PCS after the low dose dexamethasone suppression test (LDDST).
Methods
Persons with a suspicion of CD based on mild clinical features and a positive first-line screening test were included. They underwent a dex-CRH test between 2010 and 2020. Adrenal causes of hypercortisolism and women using estrogens were excluded. Those with a positive dex-CRH underwent neurosurgery. Those considered as PCS needed to be followed for at least 2 years and not develop new Cushingoid features.
Results
Dex-CRH was performed in 36 cases (F: 24) with a median age of 50 years (IQR; 32-56). Thirteen cases were diagnosed with CD (F: 11), 22 with PCS (F: 13) and 1 had an indeterminate result. The following Cushingoid features were present in cases diagnosed with CD vs PCS: moon face (15 vs 14%), buffalo hump (38 vs 27%), striae (0 vs 9%), myopathy (64 vs 19%), hypertension (54 vs 45%), type 2 diabetes (23 vs 23%) and BMI $>$ 30 kg/m^2 (46 vs 77%). 7/13 CD cases had a biochemical mild form (UFC $<$2xULN). UFC was mildly elevated in 16/22 of the PCS group and clearly elevated ($\geq$ 2x ULN) in 4/22 cases. Using a cut-off value of 38 nmol/l, LDDST was positive in 12/13 cases with CD and in 0/22 with PCS and the ensuing CRH-stimulation was positive in respectively 13/13 vs 1/22 cases. Mean serum cortisol level after LDDST in the CD group was 226.5 nmol/l compared to 16.8 nmol/l in the PCS group. After dex-CRH test mean serum cortisol was 433.1 nmol/l compared to 18.8 nmol/l, respectively. Increasing the cut-off value to 87 nmol/l led to exclusion of al PCS cases but also misdiagnosis of 1 CD case.
Conclusions
The prevalence of various Cushingoid features between mild CD and PCS was quite similar except for myopathy being more prevalent in CD. The majority of cases with PCS were obese (77%). LDDST had a good diagnostic accuracy (sensitivity 92%, specificity 100%, PPV 100%, NPV 96%). Additional CRH stimulation improved the sensitivity (100%) but had a negative effect on the specificity (95%). In conclusion, Dex-CRH test with a cut-off value of 38 nmol/l is a good test to differentiate between mild forms of CD and PCS.

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Genetic Analyses Of 20 Turkish FIPA Families Utilizing Whole Exome Sequencing: Preliminary Results Of A Multicenter Collaborative Study

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Objective
Hereditary pituitary adenomas (PAs) are rare and occur either isolated or as part of a syndrome. Familial isolated pituitary adenoma (FIPA) is the presence of only PA in at least two members of a family, where "Aryl hydrocarbon receptor interacting protein-*AIP*" gene mutations have been identified in 10-20% of cases. However, the cause of tumorigenesis in the majority is unknown. We aimed to identify novel genetic variants in a cohort of FIPA patients from Turkiye.
Materials and Methods
Twelve centers in various geographical regions of the country were included. FIPA cohort involving 20 index cases and 17 affected relatives were recruited. Whole exome sequencing was performed on 20 cases on Illumina NextSeq550 system. Bioinformatic analyses and variant prioritization at MAF$<$1% were performed, where variants for PA-related genes followed by novel candidate genes were filtered. Affected relatives were utilized in confirmation of candidate variants by Sanger sequencing.
Results
Our cohort consisted of 10 homogeneous (index cases: 4 prolactinomas/6 acromegaly) and 10 heterogeneous (index cases: 4 prolactinomas,3 Cushing's disease and 3 acromegaly) FIPAs. The gender distribution of indexes in each group is equal (5F/5M). The mean age at diagnosis of index cases was 38.44$\pm$13.25 years for acromegaly (n=9), 36.25$\pm$17.13 for prolactinoma (n=8), 44.67$\pm$2.31 for Cushing's disease (n=3). Eight out of 20 index cases of FIPA families were found to carry variations in PA-related genes, where a novel *AIP* variant (c.646-1G>C) was identified (Table 1). Confirmation and familial segregation are ongoing for variants in heterogeneous FIPAs.
Conclusion
Consistent with the literature, our preliminary results detected *AIP* mutation frequency as 15% in the FIPA cohort. Novel variants in our study highlight the genetic heterogeneity and phenotypic diversity of FIPA patients, which complicate the diagnosis.

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Prevalence of steatosis and organ-specific distribution of adipose tissue in patients affected by Cushing's syndrome

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Table 1 (Abstract 678)

Index case,(no)	Age at diagnosis (years/sex)	FIPA type, (PA phenotype)	PA-related gene	Chromosomal position	Variation	Amino acid change	Novelty
1	30/M	**Heterogeneous** Prolactinoma	*USP8 SDHB*	15:50,769,152 1:17,354,257	c.956C>T c.527A>G	p.(Pro319Leu) p.(Glu176Gly)	Novel Novel
2	37/M	**Heterogeneous** Somatotrophinoma	*AIP DICER1*	11:67,257,786 14:95,584,087	c.646-1G>C c.1381A>G	Splice acceptor p.(Ile461Val)	Novel Novel
3	27/M	**Heterogeneous** Somatotrophinoma	*AIP*	11:67,254,618	c.241C<T	p.(Arg81Ter)	Pathogenic*
4	44/F	**Homogeneous** Somatotropinoma	*AIP*	11:67,258,381	c.910C>T	p.(Arg304Ter)	Pathogenic*
5	32/M	**Homogeneous** Somatotropinoma	*TSC1*	9:135,781,415	c.1550G>A	p.(Arg517Gln)	Novel
6	47/F	**Heterogeneous** Corticotrphinoma	*CDH23*	10:73,570,263	c.2294C>T	p.(Ala765Val)	Novel
7	22/F	**Heterogeneous** Prolactinoma	*NF1*	17:29,562,948	c.3883A>G	p.(Thr1295Ala)	Novel
8	18/F	**Heterogeneous** Prolactinoma	*MSH2*	2:47,703,697	c.2197G>A	p.(Ala733Thr)	Novel

(*)**Clinvar database** (https://www.ncbi.nlm.nih.gov/clinvar/).

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Introduction
Endogenous hypercortisolism is associated with cardio-metabolic complications and promotes the deposition of lipids in different tissues, particularly in the liver. However, the prevalence of hepatic steatosis in patients with Cushing's syndrome (CS) has been little investigated so far and only one previous study reported a prevalence of 20% using computed tomography. The aim of the study is to evaluate the prevalence of hepatic steatosis and the organ-specific distribution of adipose tissue in patients affected by CS.
Methods
We performed a cross-sectional collection of clinical, biochemical and instrumental data (abdominal ultrasound, fibroscan, assessment of epicardial fat, supra-aortic trunks ultrasound and body composition through BIA) of patients diagnosed with CS and followed at our Endocrinology Unit.
Results
Forty-three CS patients were studied (M/F: 8/35; age 53 ± 13 years; 4: active disease, 29: disease remission, 6: disease control, 4: partial remission). The prevalence of hepatic steatosis was 49% (21/43 patients, of which 9 with moderate to severe degree), but only 1 patient showed fibroscan values consistent with significant hepatic fibrosis. The prevalence of carotid atherosclerosis was 58%, while an increase in epicardial fat was found in 37% of patients. CS patients with steatosis, when compared to those without steatosis, had a higher number of previous cardiovascular events (4 vs 0, $P=0.045$), a higher BMI (27.7 ± 5.4 vs 22.4 ± 3.3, $P<0.01$), a higher fat mass (34.8 ± 8.4 vs 24.7 ± 6.7, $P<0.01$), a higher prevalence of metabolic syndrome (57% vs 18%, $P<0.05$) and hyperuricemia (45% vs 9%, $P<0.05$). In a multivariate analysis model including age, sex, hyperuricemia and metabolic syndrome, the latter was associated with the development of hepatic steatosis (OR: 4.98, IC 1-25.65). Finally, the CS group with steatosis was compared to a group of 42 subjects with NAFLD, matched for age and sex. Compared to the latter, despite a similar prevalence of metabolic comorbidities, patients with CS showed a lower fat mass ($34.8 \pm 8.7\%$ vs $40.2 \pm 8.8\%$, $P<0.05$) and a higher prevalence of carotid atherosclerosis (62% vs 31%, $P<0.05$).
Conclusions
CS is characterized by a high prevalence of hepatic steatosis, carotid atherosclerosis and increase in epicardial fat. In these patients, metabolic syndrome is associated with the development of hepatic steatosis. At the same degree of steatosis, CS patients have a lower percentage of fat mass but an increased prevalence of carotid atherosclerosis compared to NAFLD patients, suggesting the pathogenetic role of hypercortisolism in the development of these complications.

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Impact of Setmelanotide Treatment on Reducing Hyperphagia in Pediatric and Adult Patients With Hypothalamic Obesity

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Objective
To report hunger-related results from a Phase 2 trial of setmelanotide in patients with hypothalamic obesity (HO).
Methods
A Phase 2, open-label, 16-week trial of setmelanotide in patients aged ≥ 6 to ≤ 40 years with body mass index (BMI) $\geq$95th percentile (aged <18 years) or ≥ 35 kg/m^2 (aged ≥ 18 years) and HO caused by hypothalamic damage secondary to brain tumor, surgical resection, and/or chemotherapy was performed. The primary endpoint was the proportion of patients reaching $\geq 5\%$ BMI reduction from baseline at Week 16. Change from baseline in daily hunger scores was a secondary endpoint. A daily hunger questionnaire was completed before morning meal (ie, while fasted) and setmelanotide administration each morning. Patients aged ≥ 12 years rated their past 24-hour hunger on an 11-point numerical rating scale, where 0 = not hungry at all and 10 = hungriest possible, with 3 questions assessing maximal, average, and morning hunger; patients aged <12 years used a pictorial version of the scale. Daily hunger scores were averaged weekly and compared with baseline score, calculated as the average of the 7 days before setmelanotide initiation. Hunger analyses were stratified by age (<12 and ≥ 12 years).
Results
Eighteen (13 pediatric, 5 adult) patients were included in the study. At Week 16, most (16/18) patients met the primary endpoint (88.9% [90% confidence interval, 69.0%-98.0%]; $P<0.0001$), with a mean percent change in BMI of -14.9% in all patients adhering to treatment administration ($n=17$). In patients aged ≥ 12 years ($n=11$), the mean (standard deviation [SD]) change from baseline in maximal daily hunger score was -2.9 (2.3) (percent change, -45.0% [36.3%]), in average hunger score was -3.1 (2.0) (percent change, -56.7% [35.4%]), and in morning hunger score was -2.7 (1.9) (percent change, -65.3% [35.2%]). Baseline maximal hunger scores ranged from 5.8 to 7.5; decreases were seen independent of baseline score. In patients aged <12 years ($n=5$), the mean change from baseline in daily hunger score was -1.4 (-62.0%). Treatment-related adverse events occurred in 18 patients (100%); nausea ($n=11$; 61.1%), skin hyperpigmentation ($n=6$; 33.3%), vomiting ($n=6$; 33.3%), diarrhea ($n=4$; 22.2%), and COVID-19 ($n=4$; 22.2%) were most frequently reported.
Conclusions
Patients with HO had reductions in hunger scores across all domains. These findings support continued development of setmelanotide for treatment of HO; a Phase 3 trial will begin in early 2023.

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Erythropoiesis in endogenous Cushing syndrome: sex-related and subtype-specific differences

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Context
Endogenous Cushing syndrome (CS) is associated with hematological abnormalities. Nevertheless, conflicting data have been reported on erythropoiesis. Some studies reported an association between CS and anemia in men, whereas others described erythrocytosis in affected patients. Furthermore, it is unclear whether there are CS subtype-specific changes in red blood cells (RBC) parameters.
Objective
To investigate sex and subtype-specific changes in RBC in a large cohort of patients with CS at initial diagnosis and after curative surgery.
Design
Retrospective, monocentric study including 210 patients (females, $n=162$; males, $n=48$; median age 49 and 48, respectively) with ACTH-dependent (Cushing's disease (CD), $n=85$; ectopic CS (ECS), $n=31$) and ACTH-independent CS (cortisol-producing adrenocortical adenoma, $n=46$; adrenocortical carcinoma $n=48$)). These patients were matched 1:1 for sex and age with patients suffering from either hormonally inactive pituitary microadenomas ($n=117$) or adrenal incidentalomas ($n=93$). RBC parameters were evaluated at initial diagnosis and after surgical cure of CS (at 3 months, 12 months, and ≥ 24 months).
Results
Women with active CS had higher hematocrit (median 42.3 vs 40.4%), hemoglobin (14.1 vs 13.8g/dl), and mean corpuscular volume (MCV) (91.1 vs 87.8fl) than female controls (all $P<0.005$). Women with CD showed higher hematocrit (43.3 vs 36.1%), RBC count (4.8 vs 4.0n*106/µl), and hemoglobin (14.3 vs 12.2 g/dl) than those with ECS (all $P<0.0005$). The same differences

were found if women with ECS due to malignant tumors were excluded from the analysis. Men with active CS had lower hematocrit (42.9 vs 44.7%), RBC count (4.8 vs 5.1n*106/μl), and hemoglobin (14.2 vs 15.4g/dl), but higher MCV (90.8 vs 87.5fl) than controls (all $P<0.05$). 20 out of 48 men with CS (42%) had hemoglobin levels below the normal range. In men with CS, no subtype specific differences but a negative correlation between 24h-urinary free cortisol and hematocrit, RBC count, and hemoglobin ($r=$-0.426, $r=$-0.477, $r=$-0.347, $P<0.05$) were identified. Compared to baseline, hemoglobin decreased in both women (-8.3%) and men (-5.8%) three months after remission from CS.

Conclusion

CS is characterized by pronounced sexual and subtype-specific changes in erythropoiesis. Women s with CS showed higher hematocrit and hemoglobin levels compared to controls. In contrast, men with CS had lower hematocrit/hemoglobin levels, which further decreased in the first months after remission. Therefore, anemia should be considered as a potential complication of CS in males. In females with CS, differences in RBC parameters may allow for a first subtype differentiation between CD and ECS.

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P682

A rollover study for patients who continued to receive benefit from pasireotide at completion of an earlier trial (B2412): An 8-year interim analysis

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Introduction

A robust clinical programme of 14 trials demonstrated pasireotide as an effective treatment for patients with rare endocrine disorders, including acromegaly and Cushing's disease (CD). Patients with acromegaly or CD have significant morbidity, reduced quality of life and, if inadequately treated, higher mortality risk than the general population. This 8-year interim analysis evaluated long-term safety of pasireotide treatment in patients with acromegaly, CD or other endocrine disorders.

Methods

This ongoing, open-label, multicentre study allows continued treatment for patients who completed a previous pasireotide parent trial (NCT01794793). Patients who continued receiving clinical benefit, according to the parent study investigator, entered the rollover study and remained on pasireotide. Depending on the administration route in the parent study, patients received pasireotide long-acting release (LAR; $n=303$) or subcutaneous (sc; $n=38$) as monotherapy ($n=36$), or sc combined with cabergoline ($n=2$). The primary objective was to evaluate long-term safety, determined by frequency of adverse events (AEs)/serious adverse events (SAEs).

Results

Overall, 341 patients from 29 countries have entered the study from 14 parent studies: 228 patients had acromegaly, 64 had CD and 49 had other endocrine disorders, including melanoma, dumping syndrome and neuroendocrine tumours. Median (min−max) exposure to all pasireotide formulations from rollover baseline to data cut-off and across all indications was 45.3 months (0.9–100.8). Median (min−max) dose from rollover baseline was 45.4 mg/month (5.3–128.3) with pasireotide LAR and 1200 μg/day (300–1800) with pasireotide sc. Altogether, 89 (26.1%) patients discontinued treatment, most commonly because of consent withdrawal ($n=21$, 6.2%). The most common AEs during rollover ($\geq 10\%$ in all patients) were nasopharyngitis (acromegaly $n=13$, 5.7%; CD $n=14$, 21.9%; other diseases $n=14$, 28.6%), hyperglycaemia (acromegaly $n=29$, 12.7%; CD $n=2$, 3.1%; other diseases $n=7$, 14.3%), back pain (acromegaly $n=20$, 8.8%; CD $n=7$, 10.9%; other diseases $n=8$, 16.3%) and headache (acromegaly $n=21$, 9.2%; CD $n=6$, 9.4%; other diseases $n=7$, 14.3%). SAEs were reported in 87 (25.5%) patients, most commonly cholelithiasis and COVID-19 (both $n=9$, 2.6%). Overall, 18 (5.3%) patients discontinued treatment because of AEs. Incidence of new hyperglycaemia-related AEs during rollover was low. No new safety signals were identified.

Conclusions

Hyperglycaemia is an expected AE during pasireotide treatment, often occurring in the first 3 months of therapy. These data support pasireotide as a well-tolerated long-term treatment in patients with acromegaly, CD or other endocrine disorders and affirm that patients receive long-term benefit, with a low discontinuation rate over 8 years.

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P683

Association of Pituitary Adenoma (Pa)/Pituitary Neuroendocrine Tumor (Pit-Net) and Cerebral Aneurysm: risk factors, peculiar features and management

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Rationale and aim

The incidence of intracranial aneurysms (IA) appears increased in patients with PAs/PitNETs. Changes in hemodynamics and vascular structure secondary to mass effect, inflammation, and hormonal changes (primarily, GH hypersecretion) have been suggested as risk factors. Study aim was to define typical features, timing of occurrence and treatment, and identify risk factors in patients with PA/PitNET and IA.

Patients and methods

Data of 57 cases (20 males) of IA associated with PA/PitNET, identified by screening 5,146 patients with PA/PitNET and 25,104 with IA evaluated at two referral Centers from 1998 to 2022, were retrospectively reviewed.

Results

Mean age at diagnosis was 52.6 ± 12 (range 28-84) years for PA/PitNET, 57.4 ± 11.6 (30-83) for IA. Forty-one (77.4%; 18 males) had a macroadenoma, 32 (82%) with extrasellar extension, and 24 (61.5%) with cavernous sinus invasion. IA was diagnosed after PA/PitNET in 30 (52.6%) cases, simultaneously in 17 (29.9%), before in 10 (17.5%). 50 (87.7%) PAs/PitNETs were treated by transsphenoidal surgery, 6 (10.5%) by craniotomy. Based on histology, 29.6% were lactotroph, 11.1% corticotroph, 18.5 somatotroph, 14.8% somato-lactotroph, 14.8% gonadotroph, and 11.1% plurihormonal. Six patients (10.5%) presented multiple IAs. Mean IA size was 4.8 ±3.9 (range 1-26) mm. Typical localizations were internal carotid artery (47.4%), anterior carotid artery (19.3%), and middle cerebral artery (14%); 56.1% of IA originated in proximity of the sella turcica. Treatment consisted of endovascular embolization in 17 (29.8%) patients, surgery in 4 (7.1%), clipping in 1 (1.8%), multiple treatments in 3 (5.3); 31 (55.4%) were not treated. Regarding risk factors, 20 (35.1%) patients had familiarity of aneurysm, none of pituitary adenoma; 2 (3.5%) had connective disorders; 18 (32.1%) had previously undergone sellar surgery and 8 (14%) radiotherapy. 54/57 (94.7%) patients presented ≥1 cardiovascular risk factor (i.e., smoking 47.4%, hypertension 70.2%, dyslipidemia 36.8%, diabetes 28.1%, overweight/obesity 71.7%, stroke/infarction 24.6%, other cardiovascular diseases 12.8%), 46 (80.7%) ≥2 risk factors.

Conclusions

Our study supports the need of screening for AI in patients with invasive macroadenomas, especially with previously surgery/radiotherapy, cardiovascular risk factors and GH hypersecretion.

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P684

Fibroblast Activation Protein in Patients with Growth Hormone Deficiency and Acromegaly: Before and After Treatment

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Background
It is well-known that growth hormone (GH) potently stimulates collagen turnover and it is associated with fibrosis in several tissues, but the mechanisms involved in GH-stimulated fibrosis are poorly elucidated. Fibroblast activation protein-α (FAPα) is an enzyme that can cleave collagens and is expressed almost only under pathological conditions such as fibrosis. FAPα also cleaves and inactivates fibroblast growth factor 21 (FGF21), which is a circulating hormone with pleiotropic metabolic effects. Despite their related involvements, data regarding the interaction between GH and FAPα are scarce.
Aim
To measure circulating FAPα, FGF21 components and biomarkers of collagen turnover in patients with adult-onset GH deficiency (GHD) and in patients with acromegaly before and after treatment, compared to a control group.
Methods
Serum samples obtained from 16 patients with adult-onset GHD at time of diagnosis and after GH treatment have been analyzed using immunoassays for FAPα concentration and activity, and total FGF21. Repeated serum samples obtained from 9 patients initially suspected for GHD but with a normal GH response to an insulin tolerance test serve as controls. This study is ongoing and biomarkers of collagen turnover are yet to be analyzed at time of abstract submission. Furthermore, we have obtained serum samples from 14 patients with acromegaly before and after treatment, which will be analyzed for the same parameters.
Results
Our preliminary data show that serum levels of FAPα (ng/ml) significantly increase in the GHD patients after GH treatment [135.6 (111.6-163.8) vs 168.5 (107.3-233.9), $P<0.05$], and FAPα activity (RFU/min) in serum likewise increase after GH treatment [719.0 (467.3-1104.2) vs 1277.8 (668.9-1609.4), $P<0.05$], [median (IQR)]. Total FGF21 remain unchanged after GH treatment. In the control group, FAPα concentration and activity as well as total FGF21 remain unchanged over a corresponding time period.
Conclusions
Circulating FAPα concentration and activity increase in response to GH treatment in patients with adult-onset GHD, whereas total FGF21 do not change in response to GH treatment. Further analyses in this study are ongoing, including comparable analyses in patients with acromegaly. It remains to be studied if the fibrotic and FAPα -stimulating effects of GH are causally linked.

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Panhypopituitarism in an Adult Patient with William-Beuren Region Duplication Syndrome: A Rare Case Report

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Background
William-Beuren region duplication syndrome (WBDS) is a rare multisystem disease caused by the gain on chromosome 7q and transmitted autosomal dominant, with approximately a population frequency of 1 in 13,000-20,000. The age of diagnosis is variable, but generally, it is diagnosed during childhood. It include endocrine (growth hormone deficiency) and non-endocrine (facial dysmorphology, cardiovascular problems, gastrointestinal and genitourinary problems, neurological problems, behavioral and psychiatric disorders) abnormalities.
Case
A 60-year-old female patient applied to our outpatient clinic with fatigue. She had a history of irregularly applying to another endocrinology clinic and using hydrocortisone and levothyroxine with the diagnosis of panhypopituitarism. We confirmed the diagnosis of panhypopituitarism with retrospective laboratory tests evaluation. She had primary amenorrhoea but never received hormone replacement. She had a hepaticojejunostomy due to Caroli's disease and was frequently diagnosed with cholangitis, which sometimes becomes a clinical manifestation of adrenal insufficiency. On physical examination, her height: was 145 cm, weight: was 42 kg, body mass index: was 19.9 kg/m^2, and she had no secondary sex characteristics. In addition, the patient's epiphyseal openings are still not closed. She had some characteristic facial features, including a round face, full cheeks, and thick lips. In retrospective examinations, it was seen that pituitary tissue was not seen, and the sella turcica was smaller than usual on the pituitary magnetic resonance imaging (MRI). The uterus and ovaries were absent on the pelvic computer tomography. She had also basal ganglion calcification on brain MRI, but had not hypercalcemia. Bisphosphonate treatment was started for her because of osteoporosis. A cardiac examination revealed intermittent ventricular extrasystole and moderate tricuspid regurgitation. In order to determine the genetic background of the patient, a molecular karyotyping test was performed with the microarray method on the Illumina iScan platform. Although the mutation causing the gain in the detected 7q11.23 region overlaps with WBDS, the common and different clinical reflections of our case and WBDS are compared in **Table.1**
Conclusions
GH deficiency, shown at a rate of 9% in the literature, was also present in our case. WBDS patient with panhypopituitarism was not found in the literature but was described in limited cases of WBS deletion syndrome. WBDS patients may present with variable clinics, but facial features may be suspicious for diagnosis. A complete endocrine evaluation aimed at detecting abnormalities of hypothalamus-pituitary-thyroid and adrenal axes and multisystem evaluation for other endocrinological abnormalities should be considered.

Key Words
William-Beuren Duplication Syndrome, Panhypopituitarism,
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Diagnostic criteria for the hypothalamic syndrome in childhood

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Objective
Hypothalamic syndrome (HS) in childhood is a rare condition. Its epidemiology is not well known because incidence and prevalence are related to very rare underlying diseases. In addition, different criteria for the syndrome are used across studies. Recognizing HS may be difficult, due to its rareness and variety of symptoms. Having diagnostic criteria for signs and symptoms of hypothalamic dysfunction may aid in early recognition and diagnosis, in the reporting and understanding of its etiology, in predicting its course and its management. We aimed to define diagnostic criteria for hypothalamic dysfunction and a score for the presence of HS in childhood.
Methods
Diagnostic criteria for hypothalamic dysfunction were developed and subdivided into hyperphagia, hypophagia, body mass index, behavioral problems, sleep disorders, temperature regulation disorders, pituitary dysfunction, Muller grading and presence/suspicion of a hypothalamic genetic syndrome. Subsequently, the scoring system was tested in a retrospective cohort of 120 patients at risk for hypothalamic dysfunction.
Results
A score for presence of HS was developed. Using this new hypothalamic score, in total 52.5% were scored as having HS. Of these patients, 76.7% were diagnosed with pituitary dysfunction, 32.5% with hyperphagia, 40% with sleep disorders and 14.2% with temperature dysregulation. For several criteria, clinical data was missing in more than 50% of cases.
Conclusions
The here proposed diagnostic criteria and score for presence of HS may be used for care purposes and will aid in early recognition. Also it will be useful for research or registration purposes.

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Smartphone App on Follow-up of Adult Growth Hormone Deficiency (AGHD) Patients: Results From the Management of AGHD (MAGHD) Study

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Background
AGHD significantly impacts on metabolism, body composition and quality of life (QoL), including sexuality.
AIM
To investigate the impact of a smartphone App on AGHD monitoring, especially QoL and comorbidities as well as on both body composition and biochemical parameters.
Methodology
83 AGHD patients were enrolled in this prospective, open-label, monocentric study (MAGHD Study) of 24-month duration. Patients were evaluated (clinical, biochemical and multidimensional investigations) every 6 months, for a total of 5 visits (from V0, V1, V2, V3 e V4). Multidimensional evaluation included the following questionnaires: QoL-AGHDA, QLS-H, WEMWBS, IPAQ, PSQI e IIEF-15 e FSFI for QoL and sexual function. Body composition was evaluated at V0, V2 and V4 by DEXA. After the first year (Phase 1), patients were grouped according to the acceptance to use (Group 1) or not (Group 2) the smartphone App (MAGHD App) for answering questionnaires. Thus, during the second year (Phase 2), 58 patients provided questionnaires answers through MAGHD App (Group 1) and the remaining 25 patients continued with standard compilation of questionnaires only at visits every 6 months without using MAGHD App (Group 2).
Results
The use of the MAGHD App resulted in a higher number of completely filled questionnaires in Group 1 (15.68 ± 8.10) compared to Group 2 (10.33 ± 2.09) ($P < 0.001$). QoL-AGHDA ($P = 0.001$), QLS-H ($P = 0.030$), IPAQ ($P < 0.001$), IIEF-15 ($P = 0.005$) and FSFI ($P = 0.002$) scores were significantly better in Group 1 than Group 2. Compliance to r-hGH therapy increased in Group 1 comparing Phase 1 to Phase 2, but without statistical significance ($P > 0.05$). Comorbidities resulted increased in number in Group 2 compared to Group 1 ($P < 0,05$). No differences were found between Group 1 and 2 in biochemical and hormonal outcomes.
Conclusions
The use of an *ad hoc* designed smartphone App is well-accepted by patients and associated with a good adherence in its use, suggesting positive effects on QoL in AGHD patients. The integration of a smartphone App in the clinical practice is feasible and may help empowering patients with chronic diseases such as AGHD on daily self-monitoring of their disease trend, beyond helping physicians in tailoring the clinical management. This study belongs to the Pfizer Inc. "Independent Grant for Learning and Change, Dissemination & Implementation' (Grant ID 34515061).

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Incidental pituitary macroadenoma: natural history and surgical results

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Introduction
The Incidental diagnosis of non-functioning pituitary macroadenomas (NPFMA) is becoming more prevalent with the spread of modern imaging techniques. More clinical data about their natural history and surgical results are needed.
Methods
We retrospectively analyzed medical files of patients referred to our clinic for an incidental NFPMA between 2010 and 2019. In particular, we compared patients that experienced tumor growth or not during surveillance, and surgical results in patients who had deficits or not at surgery.
Results
We included 65 patients (mean age $\pm$ SD: 60 $\pm$ 14 years; mean maximal diameter: 20.0 $\pm$ 7.3 mm). 44% had pituitary hormone deficits (LH/FSH 41%, TSH 29%, ACTH 15%) and 12% had visual field deficits. 26 patients had early surgery and 13 had delayed surgery after initial surveillance. In the surveillance group ($n = 35$), the risk of tumor growth was estimated at 10%/year (median time of 57 months to reach 50%). Patients with hormonal deficit at diagnosis tended to experience earlier growth ($P = 0.082$). Overall surgery led to stable or improved endocrine function in 91% (31/34) of patients, with only 6% (2/34) post-operative permanent diabetes insipidus. Surgery was more effective in preserving intact endocrine function (10/12) than restoring altered endocrine function to normal (6/22, $P = 0.03$),
Conclusion
Incidental NFPMA are often responsible for unrecognized endocrine and visual deficits and require careful evaluation. If surveillance is chosen, the risk of growth is significant (10%/year) and seems to occur faster in patients already harboring an endocrine deficit. Early surgical removal before endocrine deficits occur might lead to better endocrine outcome.

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Abstract withdrawn

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Evaluation of Serum Omentin-1 Levels and Atherosclerotic Risk Factors in Patients with Prolactinoma

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Background
Prolactinoma is the most common functioning pituitary adenoma. Subclinical atherosclerosis and cardiovascular risk in patients with prolactinoma were reported but have not been clarified yet.
Aim
Our study aims to compare prolactinoma patients with a control group in terms of lipid profile, body fat distribution, and subclinical atherosclerosis markers.
Methods
This single-center, prospective study included 32 patients diagnosed with prolactinoma and 32 control groups with similar clinical features. Patients newly diagnosed with prolactinoma were evaluated before and 6 months after treatment. Patient and control groups were compared according to their serum omentin-1 levels, lipid profile, body fat ratio, epicardial adipose tissue thickness (EATT), and carotid intima-media thickness (CIMT).
Results
25 of the patients were diagnosed with microprolactinoma, 7 with macroprolactinoma, 25 were female and 7 were male. Similar omentin-1 levels were found in prolactinoma and control groups ($P = 0.368$). A total of 20 patients, 15 female, and 5 male, were re-evaluated after the treatment. The mean omentin-1 levels of 20 patients evaluated six months after the treatment was not significantly different from the pre-treatment level ($P = 0.526$). The median EATT in the patient group which was higher than in the control group ($P = 0.021$) significantly regressed and was found similar to the control group six months after treatment ($P = 0.036$, $P = 0.248$; respectively). The median CIMT which was similar between patients and control groups ($P = 0.723$), was significantly regressed ($P = 0.040$) after treatment. In terms of median body fat rate, total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglyceride levels were found to similar between patient and control groups ($P = 0.445$, $P = 0.079$, $P = 0.200$, $P = 0.056$, $P = 0.243$; respectively). In the control group, prolactin levels were negatively correlated with EATT, CIMT, BMI, waist-hip ratio, and age ($P = 0.025$, $P = 0.006$, $P = 0.029$, $P < 0.01$, $P = 0.021$; respectively).
Discussion
Increased EATT plays a role in the development of coronary and myocardial disease, as a result of inflammation and fibrosis. CIMT is commonly used in the follow-up of subclinical atherosclerosis. In our study, EATT was found significantly higher in untreated prolactinoma patients than in the control group while CIMT was found similar. After the treatment, EATT and CIMT values,

which are two subclinical atherosclerosis markers, decreased significantly. Our results show that hyperprolactinemia is associated with subclinical atherosclerosis. More comprehensive studies are needed to evaluate cardiovascular risk in prolactinoma patients.

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Diabetes Mellitus Secondary to Cushing'S Disease or Acromegaly: a Single-Centre Experience

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Rationale
Type 2 diabetes mellitus (DM) is common in patients with Cushing's disease (CD) and Acromegaly (AC), and contributes to increased mortality. This study aimed at investigating the prevalence and characteristics of DM in CD and AC patients at diagnosis and after disease control (DC).
Patients and Methods
34 CD patients (8M,26F, 24 microadenomas(mA),6 macroadenomas (MMA) and 4 empty sella) and 35 AC patients (16M,19F, 7 mA,28 MMA) were included in the study. Anthropometric, biochemical and hormonal parameters, tumor size (TS), disease and DM duration were registered in the entire patient cohort.
Results
At diagnosis, among CD 22 patients had DM (64.6%), 10 IGT/IFG (29.4%) and 2 NGT (6%). In CD patients without DM, ACTH correlated with weight ($r=0.71$, $P=0.001$) and HOMA-IR ($r=0.72$; $P=0.02$); serum cortisol (SC) with total cholesterol (TC, $r=0.73$, $P=0.007$), and urinary free cortisol (UFC) with fasting glucose (FG, $r=0.81$, $P=0.009$) and HbA1c ($r=0.71$, $P=0.02$). In patients with CD and DM, age at onset correlated with HOMA-IR ($r=0.53$, $P=0.019$) and HbA1c ($r=0.49$, $P=0.03$). In the entire CD cohort, ACTH was the best predictor of insulin levels (FI, $P=0.004$). At diagnosis, among AC 16 patients had DM (45.7%), 17 IGT/IFG (48.5%) and 2 NGT (5.8%). In AC patients without DM, age at diagnosis correlated with TS ($r=-0.71$, $P<0.001$) and FG ($r=0.47$, $P=0.04$), and GH with TC ($r=0.73$, $P<0.001$). In the entire AC cohort, age at onset correlated with weight ($r=-0.37$, $P=0.02$), waist circumference (W, $r=-0.34$, $P=0.04$) and FI ($r=-0.37$, $P=0.04$), while GH with TC ($r=0.63$, $P<0.001$) and triglycerides (TG, $r=0.8$, $P<0.001$). 26 CD (76.4%) and 30 AC (85.7%) were re-evaluated at DC, and all had DM. At DC, age correlated with UFC in CD ($r=-0.42$; $P=0.03$); in AC, FG was significantly higher ($P=0.007$) and TG lower ($P=0.04$) in patients treated with somatostatin analogues (SRL) than in those treated with SRL + pegvisomant (PEG).
Conclusions
In CD patients, ACTH and SC influence glucose and lipid metabolism, while UFC affects mainly glucose metabolism, and ACTH is the best predictor of FI. In AC patients, GH impact on glucose metabolism adds to the detrimental effect of ageing. Despite achieving disease control, the metabolic damage was only partially reverted in CD, suggesting a mechanism of IR independent of hormonal correction; in AC, DC allows the most pronounced IR improvement, especially in PEG-treated patients.

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Characterisation of the clinical and biologic behaviour of acromegaly caused by pluri-hormonal tumours in a cohort of 75 patients

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Introduction
The clinical and biochemical spectrum of pituitary acromegaly is wide and variable. There are pure somatotroph tumors(ST), immunohistochemically positive only for GH, and pluri-hormonal(PL), also positive for other hormones, and they appear to have different presentations and responses to treatment.
Aims
To compare the clinical presentation, imaging characteristics and response to treatment of acromegalic patients according to the pituitary tumour histopathology.
Descriptive statistics
From the 75 patients, 66.7%($n=50$) were female with mean age at diagnosis of 48.8 ± 12.7 years. At diagnosis, 79.2%($n=57$) had acromegaloid phenotype, 60.9%($n=39$) presented with headaches and 39.3%($n=24$) suffered from visual impairment. Hypertension (39,2%), diabetes/pre-diabetes (35.1%) and obstructive sleep apnea (24.3%) were the most prevalent comorbidities. Regarding the biochemical profile, 88% patients ($n=66$) had functioning tumors: 77.3% ($n=51$) of these producing only GH, 19.7% ($n=13$) GH plus prolactin and 1 case produced GH plus ACTH. 33.3% patients($n=25$) had pituitary hormone deficiencies at diagnosis: hypogonadism being the most common (32.4%). In the MRI, 77.3%($n=58$) had a macroadenoma. Postoperative remission (nadir GH $<1\mu g/l$) occurred in 29.3%($n=22$) and 32% patients($n=24$) developed new pituitary insufficiencies, mainly adrenal insufficiency (16%). In the anatomopathological analysis, 64%($n=48$) were pure ST and 36% ($n=27$) were PL.
Results
There were no differences between ST and PL in terms of age (47.5 ± 12.2 vs. 48.9 ± 13.7 years), comorbidities, and pituitary hormone deficiencies at diagnosis or MRI-adenoma dimensions (19 ± 10.3 vs. 25.4 ± 14.4 mm, respectively). However, ST had greater GH levels at diagnosis than PL: 9.9(IQR 22.5) *vs.* 4.6(IQR 11.8) times above the upper limit of normal($P=0.043$). PL were more often non-functioning: 22.2%($n=6$) *vs.* 4.2%($n=2$): $P=0.045$. ST also had greater suprasellar extension(56.3%) than PL(33.3%): $P=0.009$. PL showed greater sphenoid sinus invasion: 25.9% vs. 6.3% ($P=0.03$). There was no statistically significant difference in cavernous sinus invasion between ST and PL. Sparsely granulated tumors(SG) tended to show greater compression of the optic chiasm ($P=0.05$) than densely granulated(DG). There were no statistically significant differences in immediate and long-term post-operative remission and relapse between ST and PT, and between DG and SG. However, DG had better response to medical treatment given after surgery: 61.5% had parcial/complete responses (defined as IGF-1 reduction $\geq$ 50%/normalization, respectively) *vs.* 41.7% in sparsely granulated tumors($P=0.03$).
Conclusions
In this cohort, PL had lower GH levels at diagnosis, more frequently were non-functioning and more frequently had sphenoid sinus invasion, but this was not reflected on the remission rates. Therefore, PL tumours appear to have different biologic behaviour than ST, but the clinical implications of these findings require further clarification.

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P693

Characterizing the expression of thyroid hormone transporter MCT8 for the treatment of Allan-Herndon-Dudley syndrome

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Allan-Herndon-Dudley syndrome (AHDS) is a genetic disorder characterized by intellectual disability and movement disorders. AHDS patients have mutations in the monocarboxylate transporter 8 (MCT8) that impedes thyroid hormone (TH) transport to the brain during crucial phases of brain development. In mice, the resulting structural and functional pathologies of human AHDS patients can be mimicked by knocking out murine MCT8 and the Solute Carrier Organic Anion Transporter Family Member 1C1 (SLCO1C1). Murine models such as these will thus guide us in understanding the disease and in finding AHDS treatments. To investigate the expression pattern of MCT8 we employed antibody stainings and a novel MCT8-Cre line, backed by analysis of single cell RNA sequencing data. MCT8 immunofluorescence showed strong expression in the choroid plexus and in tanycytes, both in the adult brain as well as in the embryonic and early postnatal brain. At postnatal day P8, neuronal MCT8 expression was strong enough to be detected in the cortex and hippocampus. Next, to visualize MCT8-expressing cells using an antibody independent method, we generated a new MCT8-Cre knock-in mouse and crossed it with CAG-Sun1/sfGFP mice that express a GFP-marked nuclear lamina protein only after Cre-mediated stop-cassette-excision. Fluorescence microscopy of adult brains showed reporter expression in virtually all nuclei. This near ubiquitous fluorescence suggested very early embryonal

activation of MCT8 which happens after the blastocyst stage, since they show no fluorescence. Indeed, using publicly available single cell RNA sequencing data we saw that MCT8 expression starts at but not before E5.25, which coincides with implantation. To trace MCT8 expressing cells in later stages of the developing embryo, we currently investigate an alternative strategy based on a tamoxifen-inducible MCT8-CreERT2 line. Last, we wanted to explore potential treatment options against AHDS by attaching TH to peptides targeting the brain. As delivery peptide, we used a 13 amino acid derivative of leptin, a hormone secreted by fat tissue that acts as satiety signal in the hypothalamus. Leptin enters the brain via the leptin receptor (LepR), which like MCT8 is highly expressed in the choroid plexus and tanycytes. First, we compared the ability of leptin and the leptin derivative to bind and activate the LepR. However, while leptin showed strong activity, the leptin derivative was inactive, highlighting the need for peptides with better binding and uptake characteristics.

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P694

Management challenges of gestational pituitary adenoma

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Pituitary apoplexy is a rare condition and gestational pituitary apoplexy (GPA) is even more exceptional. Clinical presentation of GPA is often non-specific overlapping with other conditions, making its diagnosis challenging. Additionally, therapeutic management is often limited since it depends on both the mother's and the fetus's prognosis. Herein we report of a woman who was diagnosed with GPA and we discuss the management of her case. A 34-year-old woman with no notable familial nor personal medical history, presented with severe headaches of sudden onset, paroxystic and holocranial associated with a blurred vision predominantly at the left eye. Her symptomatology appeared for the first time in the second trimester of her first pregnancy. Six weeks later, she consulted a neurologist. An MRI showed the presence of a pituitary macroadenoma of 21*16 mm, hyperintense T1 and hypointense T2, with hemorrhagic necrosis and abutting the optic chiasma. The patient was admitted therefore in our department of Endocrinology. Hormonal evaluation concluded to the presence of corticotropic and thyrotropic insufficiency. As hormonal changes occur in pregnancy, evaluation of secreting adenoma is mostly challenging. Nonetheless prolactin level was evaluated, demonstrating a high level of 965 ng/ml, surpassing 600 ng/ml which the maximum level of prolactin found in pregnant normal women. Thus, a substitutive treatment with levothyroxine and hydrocortisone was started. Since the patient's neuro-ophthalmologic status was stable, urgent surgery was not indicated. Bromocriptine was prescribed to our patient at progressive doses. The evolution under treatment was marked by the relief of her headaches and the improvement of her visual acuity. The delivery was successful and the baby as well as the mother were normal. GPA is an exceptional finding. Both hormonal evaluation of hypopituitarism and hypersecreting adenomas can be challenging. Therapeutic approach depends essentially on the patient's symptomatology and pregnancy term.

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P695

Sporadic neuroendocrine neoplasm: a survival analysis in a monocentric cohort

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Introduction
Neuroendocrine neoplasms (NEN) are heterogeneous tumors, usually sporadic and non-functioning, with a favorable long-term prognosis if localized. Metastases are common and survival outcomes of metastatic patients (pts) is worse than in localized disease.
Aim
To investigate survival outcomes in a monocentric cohort of sporadic NEN.
Materials and Methods
Clinical data of pts with histologically confirmed sporadic NEN, referred to the Endocrinology Unit of Federico II University of Naples from 2012 to 2023, were evaluated retrospectively. The Kaplan-Meier method and log-rank test were used for survival analysis and comparison between groups.
Results
We included 272 pts (137 females/135 males; 50.3%/49.7%) with sporadic NEN, mean age at diagnosis 55.3 years (11-89). Mean follow up was 46.19 months (m) (range 3-276). NEN were identified as incidentalomas in 64 pts (23.5%), due to symptoms in 139 (51.1%) and after surgery in 39 (14.3%); the majority were non-functioning (245; 90%). The most common primary site was pancreas (73, 26.8%), followed by lung (47, 17.3%), and stomach (41, 15.1%); liver was the main metastatic site (80, 29.4%). Grading was G1 in 125 patients (45.9%), G2 in 118 (43.4%) and G3 in 29 (10.7%). Metastatic disease was found in 125 pts (45.9%) and with significant prevalence in male ($P<0.03$). G1 prevalence was significantly higher in non-metastatic group (M-) (48.3% vs. 27.2%, p: 0.0005); G2-3 prevalences were significantly higher in metastatic group (M+) (respectively 46.4% vs. 32.6%, p: 0.024 and 18.4% vs. 4 %, p: 0.001). Surgery was performed in 134 of 272 pts (50.9%). Mean overall survival (OS) was 46.2 months (m) in M+ and 56.8 m in M-. Kaplan Meier analysis showed a better survival in M- than M+, with no difference between genders (female $P=0.001$ and male $P<0.001$). Moreover, a better OS was observed in pts who underwent surgery ($P=0.001$) and in this subgroup metastases did not show a significant impact on OS ($P<0.001$).
Conclusions
These data prove that surgery improves OS in metastatic NEN, regardless of the presence of metastases, maybe due to reduced tumor burden. Moreover, metastatic disease is mainly associated with male gender and G2-3 with liver as main metastatic site.

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P696

In the Phase III studies LINC 3 and LINC 4, osilodrostat was effective and well tolerated in patients of Asian and non-Asian origin with Cushing's disease

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Introduction
Osilodrostat (oral 11β-hydroxylase inhibitor) demonstrated rapid, sustained cortisol normalisation in Phase III studies (LINC 3, NCT02180217; LINC 4, NCT02697734) in patients with Cushing's disease (CD). Relative osilodrostat bioavailability is ~20% higher in Asian patients than other ethnicities; body weight is not a major determinant of this difference. This analysis of LINC 3 and LINC 4 evaluated osilodrostat efficacy and safety in Asian and non-Asian patients with CD.
Methods
Data were pooled from LINC 3 and LINC 4. LINC 3 comprised a 48-week (W) core phase, including an 8W randomised withdrawal for eligible patients. LINC 4 included an upfront 12W, double-blind, placebo-controlled period followed by 36W of open-label osilodrostat. Both studies had an optional extension. Outcomes were evaluated separately in Asian and non-Asian patients. Periods where patients received placebo were excluded.
Results
In total, 56/210 (27%) patients were of Asian origin, enrolled in China ($n=16$), South Korea ($n=14$), Japan ($n=9$), Thailand ($n=9$), India ($n=7$) and USA ($n=1$). Most non-Asian patients were Caucasian ($n=138/154$, 90%). Median (min−max) osilodrostat dose was 3.8 (1−25) and 7.3 mg/day (1−47) in Asian and non-Asian patients, respectively. Mean urinary free cortisol (mUFC) control was achieved at W48 and W72 in 64.3% and 68.1% of Asian and 68.2% and 75.8% of non-Asian patients, respectively. Improvements from baseline in most cardiovascular and metabolic-related parameters and physical manifestations of hypercortisolism were similar across groups during treatment. Osilodrostat was generally well tolerated. The most common investigator-reported adverse events (AEs) were: adrenal insufficiency

(44.6%), nausea (33.9%) and decreased appetite (26.8%) in Asian patients; nausea (45.5%), fatigue (40.9%) and headache (39.0%) in non-Asian patients. The most common serious AE in Asian and non-Asian patients was adrenal insufficiency (5.4% and 5.2%, respectively). Hypocortisolism-related AEs occurred in 58.9% of Asian and 40.3% of non-Asian patients, commonly reported by study investigators as adrenal insufficiency (44.6% and 22.1%). AEs related to pituitary tumour enlargement occurred in 21.4% of Asian and 9.1% of non-Asian patients. Arrhythmogenic potential and QT prolongation AEs were infrequent in all patients.
Conclusions
Osilodrostat demonstrated similar beneficial effects in Asian and non-Asian patients in mUFC control and improvements in cardiovascular and metabolic-related parameters and physical manifestations of hypercortisolism. The mean dose to achieve beneficial effects was lower in Asian than non-Asian patients. Osilodrostat was generally well tolerated in Asian and non-Asian patients; AEs related to hypocortisolism and pituitary enlargement were more frequent in Asian than non-Asian patients.

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P697

Transphenoidal surgery for sellar and suprasellar lesions: a prospective analysis of factors affecting inpatient length of stay

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Background
The recent Get It Right First Time (GIRT) report suggests short stay pathways should be aimed for in pituitary surgery in England, with 1–2 days being realistic. We prospectively audited the length of stay (LOS) for patients undergoing transsphenoidal surgery (TSS) for sellar and suprasellar lesions at the Royal Victoria infirmary hospital (RVI) over a 2-year period, from October 2019.
Methods
Data was prospectively collected for each patient: demographics, LOS, post-operative complications.
Results
78 patients underwent TSS during the audit period, with a mean LOS of 9.4 days. 31% of patients suffered a post-operative CSF leak and 45% experienced post-operative serum sodium imbalances. Patients with craniopharyngioma had a longer LOS compared to those with benign pituitary tumours (13.3 vs. 8.8 days). Rates of post-operative CSF leaks were higher in patients with Cushing's disease (50%) but post-operative sodium imbalances occurred most frequently in patients with craniopharyngioma (70%). The mean LOS, for two-thirds of patients with non-functioning pituitary adenomas or acromegaly with no post-operative complications, was 5 days. Older patients (aged >60 years) were more likely to have longer LOS at 12 days (vs. 6 days) and were more likely to suffer from post-operative CSF leak (38% vs. 18%) and electrolyte imbalances (38% vs. 21%). Patients on four or more regular medications, a marker of comorbidities, stayed 1.5 times longer in hospital than those on less regular medications. On average, post-operative sodium imbalances occurred 2 days after surgery and took 7 days to resolve.
Conclusions
LOS for patients undergoing TSA for sellar and suprasellar lesions is influenced by the etiology of the lesion, age of the patient, existing comorbidities and post-operative complications. Younger patients with non-functioning pituitary adenoma or acromegaly should be the more realistic cohort to aim for shorter LOS.

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Evaluation of the Association of Primary Empty Sella Syndrome in Neurobehçet Syndrome

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Central nervous system involvement is observed in 5-14% of Behçet's disease and this form is called neurobehçet syndrome (NBS). There are two main forms of CNS involvement in Neurobehçet syndrome, in which parenchymal involvement and vascular involvement are prominent. Cerebral venous thrombosis (CVT), the most prominent form of vascular involvement, has been reported in 8% in Behçet's disease and in approximately 18% in NBS. Although CVT is the most common cause of intracranial hypertension in Behçet's disease, it can also manifest as a form of idiopathic intracranial hypertension in the absence of cerebral venous thrombosis. In this study, it was thought that these patients are in the risk group for the development of empty sella due to the risk of developing intracranial hypertension, which is not uncommon in patients with neurobehçet syndrome. The files and electronic data of 732 patients with behçet's who were followed up in Eskişehir Osmangazi University Rheumatology Polyclinic between 2000-2021 were retrospectively scanned, and 74 patients with neurobehçet's diagnosis were recruited from these patients. Gender of the patients, age at diagnosis, time elapsed between the diagnosis of neurobehçet syndrome and the diagnosis of Behçet's disease, time spent as Behçet's disease, the form of neurological involvement, the initial symptom of neurological involvement, the localization of the vessels involved in vascular NBS patients, the presence of empty sella and cases with primary empty sella. The pituitary hormone profile was examined. Of the 74 patients included in the study, 31 (41.9%) were female and 43 (58.1%) were male. In our study, 32 (43.2%) patients with parenchymal neurobehçet syndrome and 42 (56.8%) patients with vascular neurobehçet syndrome were found among neurobehçet syndrome patients. Empty sella was detected in 19 (25.6%) of 74 patients in our study. Of the empty sella ($n=19$) cases, 13 (68.4%) were vascular and 6 (31.6%) were parenchymal patients. There was no statistically significant difference between these two groups in terms of the presence of empty sella. Hypopituitarism was detected in 2 of the cases accompanied by primary empty sella syndrome.

Keywords: neurobehçet, empty sella, intracranial hypertension, hypopituitarism
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P699

Non-functioning PitNETs: positive or differential diagnosis?

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Introduction
Clinically non-functioning pituitary neuroendocrine tumours (NFPitNETs) include all anterior pituitary tumours that are not hormonally active. In histopathology (HP) and immunohistochemistry (IHC), most of NFPitNETs are gonadotroph (1). Immunolabeling is negative in only 10% of cases ('null-cell'). Occasionally, NFPitNETs are positive for GH, PRL, TSH or ACTH despite absent or only minimal secretion of these hormones *in vivo*, which are known as silent somatotroph, lactotroph, thyrotroph or corticotroph tumours.
Materials and methods
The study included 27 patients with NFPitNETs, with a male:female ratio of 19:8 and a median age at diagnosis of 51.8 years (($\pm$13,7). The HP-IHC features were correlated with the clinical, imaging and laboratory data. Tumour specimens were assessed for anterior pituitary hormones, pituitary-specific transcription factor 1 (PIT-1), T-box transcription factor (TPIT) and steroidogenic factor 1 (SF-1) transcription factors (TF), Ki-67 labelling index, vimentin and reticulin.
Results
All patients had macroadenomas (median 35.5 mm $\pm$11.9 DS), the symptoms being associated with the tumoral syndrome (70.3% had headache and optic chiasm disorder). The treatment was mostly surgical, with association of radiotherapy in 33.3% of cases. Of the 16 patients with pituitary deficiency, only 2 had remission of the deficit after surgery. Most NFPitNETs were acidophilic, with alveolar and papillary growth patterns in many cases. After the IHC evaluation of anterior pituitary hormones, the 27 NFPitNETs were reclassified, according to WHO 2022 criteria. Over half of them had positive expression of LH and/or FSH, being, in fact silent gonadotropinomas. 18.5% were hormone-negative, 11.1% expressed ACTH, 7.4% expressed GH and ACTH and 7.4% expressed GH. After IHC evaluation of pituitary TF, only 4 out of 5 tumours were, in fact, 'null-cell'. The expression of Ki-67 was $<3\%$ in all cases.
Conclusion
The clinical term 'non-functioning' is not a diagnosis, yet a description of a clinical scenario that has many differential diagnoses (2). More than 50% of clinically and biochemically NFPitNETs are silent gonadotropinomas, some of which have negative immunohistochemical expression of the hormones FSH and LH.
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P700

Grading of pituitary adenomas (PitNets): clinical and prognostic implications in a monocentric series

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Rationale
Pituitary neuroendocrine tumors (PitNets) are aggressive in 20% of cases, with local invasion, relapse/scarce response to conventional treatment, in the absence of reliable predictive parameters. In 2018, Trouillas *et al*. proposed a 5-tier prognostic classification, not widely validated yet. In our study we evaluated the outcomes of a PitNets monocentric series in the context of this classification.
Materials & Methods
We retrospectively evaluated 88 patients (51 M, 50.5 ± 14.7 yrs) with functioning (FPA) or non-functioning pituitary macroadenomas (NFPA), referred to the Endocrine Unit of Messina University Hospital, and operated by the same neurosurgeon in the period 2015-2020. Of each patient we recorded demographic, clinical, radiological, biochemical data and visual field, both at diagnosis/last follow-up (median 3 ± 1.5 yrs), therapeutical history and pathological data. Once defined the PitNets grade according to Trouillas *et al*., we correlated it to clinico-pathological features at diagnosis, and to the outcomes (last follow-up).
Results
38.6% of patients were in the 1a grade, 7.9% in the 1b, 48.9% and 4.5% among 2a and 2b, respectively. Of 10 giant PitNets, 70% were 2a. At diagnosis, panhypopituitarism and visual field alterations were higher among 2a. GH-omas were significantly prevalent among 1a tumors, NFPA among 2a. 1a and 2a grade PitNets had a better response to single surgery ($P < 0.01$), while cyberknife stereotactic radiotherapy was needed in 2a and 2b tumors. Panhypopituitarism/visual field alterations were more frequent among 2a PitNets even after surgery. Ki-67 was positively associated to persistent disease in FPA, while radiological invasion was associated to remnant presence among NFPA.
Conclusions
Invasive and not-proliferating PitNets (2a) were more frequently associated to impaired pituitary function/visual field before and after surgery. Less proliferating tumors (1a and 2a) were more responsive to surgery. Ki-67 related to disease persistence in FPA, while adiuvant radiotherapy was more used among invasive tumors. Thus, among ± 1 cm PitNets, tumor invasion influences clinico-biochemical outcomes, while Ki-67 influences surgical outcomes.

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P701

Emergence of De-novo Steroid-Responsive Conditions Following Remission of Cushing's Syndrome: A Case Report and Scoping Review

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Background
Endogenous Cushing's syndrome is caused by chronically elevated glucocorticoid levels. The most common etiology is ACTH hypersecretion from a pituitary adenoma; other causes include hypersecretion of cortisol from an adrenal source or ectopic ACTH secretion. Following successful treatment, a period of adrenal insufficiency is expected due to chronic suppression of the HPA axis. Onset and exacerbation of steroid-responsive conditions have been reported following remission of Cushing's syndrome, leading to challenges in distinguishing a new condition vs. expected symptomatology following remission.
Objective
Describe a case of a 44-year-old man presenting with new-onset sarcoidosis diagnosed 12 months following surgical cure of Cushing's syndrome secondary to adrenal adenoma, and synthesize existing literature reporting on de-novo steroid-responsive conditions presenting after Cushing's syndrome remission.
Methods
A scoping review was conducted in September 2022 in Medline, Epub, Ovid, and PubMed. Case reports and case series detailing adult patients with biochemical and clinical remission of endogenous Cushing's syndrome presenting with new-onset steroid-responsive conditions were included.
Results
1641 articles were screened, 138 full-text studies were assessed for eligibility, and 45 studies were included and underwent data extraction and analysis, of which 83 cases were identified. Thyroid diseases (Graves, Hashimoto's thyroiditis, subacute thyroiditis) were the most commonly reported conditions (41/83; 49%), followed by sarcoidosis (14/83; 16.8%). Psoriasis, lymphocytic hypophysitis, idiopathic intracranial hypertension, multiple sclerosis, rheumatoid arthritis, lupus, and seronegative arthritis were reported in more than one case. All patients achieved clinical remission of Cushing's syndrome following surgical management via transsphenoidal resection or adrenalectomy with or without additional medical or radiotherapy, and one patient via medical management alone. The average duration between Cushing's remission and de novo condition's symptomatology was 11 months. 57% of patients were receiving corticosteroid therapy at the time of onset.
Conclusion
First presentations of several distinct steroid-responsive conditions have been reported as following remission of Cushing's syndrome. Of these, thyroid disorders and sarcoidosis were the most commonly reported and are well-characterised in the literature. Clinicians should have a low index of suspicion for the emergence of autoimmune and inflammatory conditions in the first year following surgery or initiation of treatment of Cushing's syndrome.

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P702

A Low Incidence of Transient Anti-Drug Antibodies Is Observed Upon Long-Term Exposure to Lonapegsomatropin in Children With Growth Hormone Deficiency

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Objectives
Lonapegsomatropin (SKYTROFA; TransCon hGH), a prodrug of somatropin, is approved by the EMA and FDA for once-weekly treatment of pediatric growth hormone deficiency (GHD). Lonapegsomatropin uses TransCon® technology, which combines a parent drug transiently linked to an inert carrier to achieve sustained release. The characterization of anti-drug antibodies (ADAs) was assessed in 3 phase 3 trials of lonapegsomatropin in pediatric GHD.
Methods
Samples were collected at baseline and at 13-week intervals and analyzed for the presence of ADAs using validated immunoassays. Bridging ELISA, a bridging ECLIA, and an indirect ECLIA assay were set up to assess ADAs against human growth hormone (hGH), lonapegsomatropin (prodrug), and mPEG (carrier), respectively. A cell-based proliferation assay was used to assess the presence of neutralizing anti-hGH antibodies. Analysis of ADAs was performed on samples from 305 participants, with a mean duration of treatment of 3 years (157 weeks (data cutoff date: September 1, 2021)).
Results
No neutralizing antibodies were detected at any time point. At baseline, 1.3% of participants had positive results for anti-hGH antibodies. Treatment-emergent or treatment-boosted anti-hGH antibodies were detected in 5.2% and 0.3% of participants, respectively. Anti-mPEG antibodies at baseline were detected in 2.8% of participants, treatment-emergent anti-mPEG antibodies in 0.7% of participants, and no treatment-boosted anti-mPEG antibodies were detected. Anti-lonapegsomatropin antibodies were detected in 0.4% of participants at baseline, and 4.3% of participants were positive for treatment-emergent anti-lonapegsomatropin antibodies. All antibody titers were low (≤ 400). Antibodies were considered transient, and primarily appeared within 6 months of treatment initiation.
Conclusions
Lonapegsomatropin did not give rise to neutralizing antibodies, and no impact of binding ADAs on efficacy or safety was observed in any of the 305 participants with pediatric GHD. With an average of 3 years of trial participation, these data support the safety of long-term treatment with lonapegsomatropin.

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Diabetes insipidus in children secondary to a germinoma diagnosed after 3 years of follow-up

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Central diabetes insipidus (CDI) is rare in children and has a wide variety of causes. In children, the majority of central DI is acquired, but 30 to 50% is considered idiopathic. However, the natural history of isolated idiopathic central ID is unpredictable and germinoma should always be considered during the first 3 years of follow-up.

Case report

We report the observation of a 16 year old patient, in whom the diagnosis of idiopathic central diabetes insipidus was retained in front of a polyuro-polydipsic syndrome with hypotonic urines and a restriction test in favour of a complete deficit, without antehypophyseal involvement, the morphological exploration (hypothalamo-hypophyseal MRI) did not objectify any intrasellar process, nor thickening of the pituitary stalk with absence of visualization of the post pituitary. The etiological exploration came back without anomaly. The patient was regularly followed by hormonal and morphological evaluation every 6 months. During the follow-up, a corticotropic deficit appeared after 2 years and morphologically an intrasellar process 30×16×24 mm was found after 3 years of monitoring, in comparison with bHCG and apha protein not elevated. In this context the patient benefited from a surgical management, the anathomo-pathological study came back in favor of a dysgerminoma. The treatment was completed by chemotherapy and radiotherapy, the patient is currently in remission for 2 years.

Discussion

This observation reminds the necessity of strict surveillance of patients with a diagnosis of idiopathic retained central diabetes insipidus, This joins the cohort of D. Lorgi in 61 children with diabetes insipidus considered idiopathic at diagnosis and prospectively followed by regular imaging, 11 finally had a diagnosis of germinoma or histiocytiosis within 2.5 years.

Conclusion

Once a diagnosis of CID is made, an etiologic investigation is necessary to tailor management. Patients with CID of undetermined etiology (idiopathic CID) require long-term clinical, radiological and biological monitoring to detect a specific etiology in time.

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Solitary pulmonary nodule developing ectopic Cushing's Syndrome over the years: Awakening of a Sleeping Giant

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Background

A rare cause of ectopic Cushing's Syndrome (ECS) is pulmonary neuroendocrine neoplasm (NEN) with a broad spectrum of clinical behavior. At the time of diagnosis, pulmonary NENs may present as occult tumors or well-defined round-to-oval lesions in close relationship to the bronchus. Herein, we describe a NEN that developed ECS three years later in a patient followed up for a solitary pulmonary nodule (SPN).

Case Presentation

A 56-year-old female patient with diabetes, hypertension, and obesity presented with complaints of excessive swelling in the hands, feet and legs for the last two months and fatigue in July 2022. Adrenocorticotropic hormone (ACTH)-dependent CS was detected in the patient whose physical examination suggested CS (moon face, buffalo hump, purple stria, and easy bruising) based on the following test results: ACTH= 149 pg/ml (reference range (RR):0-46), low-dose dexamethasone suppression test (DST)= 34.6 mg/dl, midnight salivary cortisol= 23.03 ng/ml (RR:0.7-2.2), and 24-hour urine cortisol= 1915 mg/day (RR:3-45). The presence of severe hypercortisolemia not suppressed by high-dose DST and deep hypokalemia (K^+ = 2.49 mmol/l (RR:3.5-5.1)) and the absence of any lesion on pituitary MRI suggested an ectopic focus. Subsequently, thin-slice thorax CT showed a 20 mm SPN in the middle lobe of the right lung. The retrospective evaluation revealed that the present SPN was first detected as 15 mm in June 2019. At that time, the nodule had low FDG uptake (SUVmax=2.7) in ^{18}FDG PET/CT, and a pulmonologist followed up the patient for about 2 years. During this period, the patient did not have any complaints suggesting CS. Moreover, serum cortisol level was suppressed after 1 mg DST which was examined as part of an obesity evaluation in 2019. With this clinical history, Gallium-68 PET/CT was performed but no uptake was detected. Since no extrathoracic focus was detected, a transthoracic fine-needle aspiration biopsy of the nodule was performed. Immunohistochemical studies demonstrated diffuse staining with chromogranin and ACTH and moderate staining with synaptophysin and CD56 in tumoral monomorphic epithelial cells. The absence of mitosis and necrosis in the samples suggested a typical bronchial carcinoid. During the evaluation, hypercortisolemia was controlled with metyrapone at a dose of 1250 mg/day. The multidisciplinary council made the surgical decision.

Conclusions

The present case demonstrates that a stable SPN followed without any clinical findings may actually be a NEN and may lead to ECS over time. Therefore, we believe that rare bronchial carcinoids should be kept in mind during SPN follow-up.

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P705

Isolated IgG4 Hypophysitis

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Hypophysitis is an inflammatory disorder of the pituitary gland and among them, IgG-4 hypophysitis is rare and presents in less than 5 % of cases.

Case

59 years old lady with a past medical history of asthma presented Rheumatology with? giant cell arthritis due to constant frontal headache, pain behind her eyes, and raised inflammatory markers (ESR 15, CRP 17) three weeks after COVID infection. After review, rheumatology team concluded unlikely giant cell arthritis and she was then seen by medical team who arranged MRV to exclude the central venous thrombosis due to raised BMI of 35 and recent COVID. MRV exclude thrombosis however there was a bulky pituitary gland. Subsequent MRI pituitary showed a 12 mm pituitary macroadenoma extending superiorly out of sella and contact the optic chiasm without compression or deviation. The visual field was normal. Hydrocortisone 10 mg in the morning, 5 mg in the afternoon, and 5 mg in the evening were started followed by Levothyroxine 50 mg a few weeks later. When reviewing in 2 months' time she complained of left-sided vision changes and repeated visual field showed left upper quadrantanopia. An urgent MRI showed a rapidly enlarging hemorrhagic pituitary macroadenoma with a 6 mm increase in size with increasing chiasmatic compression. Endoscopic endonasal resection of the pituitary gland was performed and she recovered well from the surgery. Histopathology of pituitary biopsy showed IgG-4 hypophysitis. Interestingly measured IgG-4 was normal – 0.57 g/l (Reference range 0.0 – 1.3). CT chest, Abdomen, and Pelvis were performed to look for systemic involvement of IgG-4 and she was referred to the rheumatology team. There were no systemic features suggestive of IgG-4 with a negative autoimmune screen and clear CT chest, abdomen, and pelvis apart from an incidental finding of an 11 cm right ovarian dermoid cyst causing hydronephrosis which has been referred to Gynaecology for further management.

Conclusion

Many cases of IgG4 hypophysitis present as a part of a multisystemic disease however it can be present as isolated primary hypophysitis. Although systemic involvement will be less common in the latter, close follow-up is required for early recognition and further management.

Results of pituitary profile blood test:

Test	Results	Reference range
T4	7.3 pmol/l	12 – 22
TSH	0.79 m IU/l	0.27- 4.20
LH	1.7 IU/l	
FSH	4.3 IU/l	
Prolactin	815 m IU/l	60-620
Cortisol	13 nmol/l	140-170
ACTH	14 ng/l	0-46
IGF-1	19.2 nmol/l	5.9-27.5

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P706

Rare causes of adrenal tumours and the possible role of adrenal arterial embolization - two case reports

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Introduction
Adrenal oncocytoma (AO) and ganglioneuroma (GN) are rare causes of adrenal masses, corresponding usually to nonfunctional and benign tumors. However, 20% of the AO shows some elements of malignancy and 10–20% of them affect adrenal hormone production. GNs account for 0.3%-2% of adrenal incidentalomas, with punctate calcifications in CT imaging being highly suggestive. However, preoperative differential diagnosis remains challenging. Adrenal arterial embolization may reduce tumor bulk and tumor vascularity; sometimes it is performed to suppress excess adrenal hormone production
Patient 1
A 57 years-old female with type 2 diabetes, dyslipidemia and hypertension presented with episodic flushing and right flank pain. Abdominal CT imaging showed a 12 cm enhancing right adrenal mass, wash-out >50%, 35 UH, diverting the right kidney and duodenoum. These findings suggested an atypical appearance. Physical exam revealed class I obesity (BMI 32,8 Kg/m2), high blood pressure (170/80 mmHg), facial and abdominal hirsutism. Blood tests revealed hypercortisolism (cortisol 5,31 mg/dl after 1 mg dexamethasone suppression test; ACTH 15,2 pg/ml) and hyperandrogenism (total testosterone 3,83 ng/ml (0,108-0,569), androstenedione >10,10 ng/ml (0,5-4,7), DHEA-SO4 >3000 mg/dl (29,7-182,2), 17 alpha progesterone 26,68 ng/ml (0,32-2,72). Renin, aldosterone and urinary metanephrines were unremarkable. The patient underwent selective right adrenal arterial embolization; 3 days later she was submitted to right adrenalectomy. Histopathology revealed an oncocytic neoplasm of uncertain malignant potential. After surgery a clinical and hormonal improvement was observed without any signs of disease persistence or recurrence
Patient 2
A 40 years-old male without relevant past medical history, presented an incidental finding in abdominal CT: a suspicious and heterogeneous 8,9 cm right adrenal lesion, with 31 UH and some punctiform calcifications, contacting but not invading right kidney and inferior vena cava. Physical exam revealed BMI 26 Kg/m2, normotensive and without stigmata. He had not any signs or clinical analysis suggesting hypercortisolism. Renin, aldosterone, urinary metanephrines and DHEA-S were normal. He underwent right adrenalectomy; histopathology revealed an adrenal ganglioneuroma (mature type). He had a good postoperative evolution.
Conclusions
In both, adrenalectomy was indicated given the large size and the imaging appearance of adrenal masses. In patient 1, hormonal production raised the suspicion for adrenal carcinoma secreting cortisol and androgens. Adrenalectomy is the gold standard for the treatment of adrenal GNs and AO. Histopathology is necessary to confirm these diagnoses, which usually have a benign prognosis. Adrenal embolization may have a role preoperatively.

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P707

Acromegaly and its ophthalmic, neurological and psychiatric complications

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Introduction
Acromegaly is a rare, complex condition that throughout its evolution affects the body on numerous levels, especially if inappropriately managed. Some of the complications it develops over time are ophthalmic, neurological and psychiatric.
Aim
The aim is to asses the impact of long-term acromegaly on the eye, nervous system and mental health of previously diagnosed patients.
Patients and method
90 patients' records (mean age 53.91 years) with previously diagnosed acromegaly, who have been assessed at least once in our tertiary referral centre (Department of Endocrinology, University Hospital 'Sfântul Spiridon', Iaşi) over a period of 7 years have been reviewed.
Results
Out of the 90 assessed patients (33 male - 36.66% and 57 female - 63.33%), 26 (28.88%) had opthalmic complications, 11 (12.22%) had neurological complications and 17 (18.88%) were diagnosed with psychiatric conditions in the context of the endocrine alterations caused by the disease. The diagnosed ophthalmic complications are as follows: partial optic atrophy in 7 patients (26.92%), total optic atrophy in 5 patients (19.23%), temporal hemianopsia in 2 patients (7.69%), quadrantanopia has been also found in 2 patients (7.69%), retinal angiosclerosis in 2 patients (7.69%), the presence of scotoma has been determined in 2 patients (7.69%), diabetic retinopathy in 2 patients (7.69%), hypertensive retinopathy grade 1 in 3 patients (11.53%), and grade 2 in 5 patients (19.23%), glaucoma in 1 patient (3.84%) and cataract in 2 patients (7.69%). Neurology-wise, a history of stroke has been reported in 4 patients (36.36%), facial palsy in 1 patient (9.09%), peripheral neuropathy has been diagnosed in 4 subjects (36.36%) and grand mal seizures in 2 individuals (18.18%). When it comes to psychiatric manifestations associated with endocrine diseases, anxiety was reported in 13 patients (76.47%), depression in 5 patients (29.41%) and delusional disorder in 1 subject (5.88%).
Conclusions
The present research has offered insight into the ophthalmic and neuropsychiatric complications frequently associated with the development of acromegaly, thus reiterating the need of an interdisciplinary approach to these patients, in order to insure correct diagnosis and treatment and an improved quality of life.

Key words
acromegaly, opthalmic complications, neuropsychiatric complications
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P708

Congenital, isolated, and lifetime growth hormone deficiency provides superior cognitive performance in senescence

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Mice with isolated GH deficiency (IGHD) due to GHRH receptor mutations live longer than their normal siblings with an extended healthspan, i.e., the period of life free from disabilities. Human IGHD individuals due to a mutation in the GHRH receptor gene from Itabaianinha, Brazil, has a normal lifespan with an extended healthspan (1). Our hypothesis is that their aging is accompanied by a delayed cognitive decline. Accordingly, we used the Literacy Independent Cognitive Assessment (LICA) in 15 IGHD individuals over 50 years of age and 15 controls matched by age, sex, years of education, and percentage of illiteracy. All individuals were negative for HIV and syphilis serology, and exhibited normal serum levels of folate, vitamin B12 and TSH. IGHD subjects had a higher total LICA score than the control group, without reaching statistical significance. However, they showed better attention ($P=0.013$) and executive function ($P=0.034$). MANCOVA revealed that group had a significant effect on attention (partial eta squared of 0.216, power of 0.749, $P=0.011$), and on the executive function (partial eta squared of 0.154, power of 0.570, $P=0.035$), translating into superior cognitive performance in the IGHD group. In conclusion, untreated lifetime IGHD is associated with superior cognitive performance in senescence.
1. Aguiar-Oliveira MH & Bartke A. Endocr Rev. 2019;40(2):575-601

Table 1 Comparison of LICA domains and total LICA score in 15 IGHD and 15 controls. Scores below 186.0 and 154.5 define dementia in literacy and illiteracy, respectively. Continuous variables compared by Student's t test and illiteracy and sex by Fisher's exact test.

Parameters	IGHD	Controls	95% CI	P
Age (years)	66.0 (8)	66.4 (6.5)	-5.8 to 5.0	0.881
Sex, male (n%)	6 (40)	6 (40)	-0.3 to -0.3	1
Weight (kg)	46.5 (15.1)	66.6 (10.3)	-29.7 to -10.4	<0.0001
Height (m)	1.2 (0.1)	1.6 (0.1)	-0.4 to -0.3	<0.0001
Head circunference (cm)	50.7 (2.8)	54.7 (2.2)	-5.9 to -2.1	<0.0001
Illiteracy (n%)	5(33.3)	5(33.3)	-0.3 to 0.3	1
Education years	6.4 (5.5)	4.7 (4.1)	-1.9 to 5.3	0.332
Memory	89.2 (19.3)	83.6(11.9)	-6.5 to 17.6	0.347
Visuospatial construction	28.0 (2.8)	26.2 (3.5)	-0.6 to 4.2	0.134
Language	39.4 (3.8)	39.4 (3.9)	-2.9 to 2.9	1
Executive function	38.3 (4.8)	35.1 (2.5)	0.3 to 6.1	0.034
Attention	9.5 (1.4)	8.3 (1.1)	0.3 to 2.1	0.013
Calculation	11.5 (0.5)	11.7 (0.5)	-0.5 to 0.2	0.373
Total Score	215.8 (22.7)	204.2 (18.1)	-3.7 to 28.0	0.130

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Adrenocortical, somatotropic and antidiuretic response to nasal glucagon in healthy subjects

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Rationale
In the diagnosis of hypopituitarism, the glucagon stimulation test allows for the simultaneous and safe evaluation of the somatotropic and corticotropic axes; recent data have highlighted a stimulating action also on the neurohypophyseal secretion of arginine-vasopressin. This procedure involves the intramuscular or subcutaneous administration of 1-1.5 mg of glucagon based on the patient's weight (respectively less or more than 90 kg). Nowadays no data are available regarding the new intranasal formulation (Baqsimi®, 3 mg single-dose nasal powder). This considered, the primary outcome of this pilot proof-of-concept study was to evaluate the anterior and posterior pituitary response in healthy subjects, in terms of changes in ACTH and cortisol, GH and copeptin levels, after administration of 3 mg of glucagon nasal powder or placebo.
Design and methods
For this non-randomized cross-over study, we recruited 10 healthy subjects (50% women) aged $\geq$ 18 years and with a BMI between 18.5 and 25 kg/m^2. Exclusion criteria were any current ongoing treatment, pregnancy and breastfeeding. All participants underwent to 2 different days of testing, when glucagon or placebo were administered intranasally in a random order. At baseline (immediately before taking glucagon or placebo), every 15' up to +90', and then every 30' up to +180' a blood sample was taken for ACTH, cortisol, GH, copeptin, glucose, insulin, sodium, potassium, plasma osmolarity. At baseline and the end of the test urinary osmolarity was evaluated as well.
Results
After administration of both placebo and glucagon ACTH and cortisol values progressively decreased over time ($P<0.001$) but in the drug group the reduction in cortisol was blunted up to +90' ($P<0.05$). GH values decreased after placebo administration ($P<0.001$) while after glucagon there was a non-significant trend towards its increase ($P=0.096$) with the difference between the two groups evident starting from +120' onwards ($P<0.005$). The placebo administration led to a reduction of copeptin ($P=0.008$), while its stability was observed after glucagon administration. Six subjects developed hypokalemia (potassium <3.5 mmol/l) post-glucagon. The potassium nadir at 45' was significantly correlated with the immediate post-glycemic rise insulin peak (Spearman's rho -0.719; $P=0.019$). No significant differences were observed regarding the other analytes tested.
Conclusions
Nasal administration of glucagon, unlike the intramuscular or subcutaneous injection, does not constitute an effective stimulus for anterior and posterior pituitary secretion, at least at the dose typically used for severe hypoglycemia. Hypokalemia secondary to hyperinsulinemic rebound appears to be a frequent complication of acute glucagon administration.

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P710

Chordomas of the parasellar region: description of 4 cases of a rare disease

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Background
Chordomas are rare, invasive and slow growing bone tumours with different locations. Parasellar chordomas are even more rare and the initial manifestations include visual and/or neurological symptoms. In addition, endocrine dysfunction may be present. We describe 4 cases of parasellar chordomas.
Clinical cases
1) Female, 55-years-old, reported headache associated with restriction of left eye movement for the past 3 months. Brain magnetic resonance imaging (MRI) revealed a solid destructive lesion in the left cavernous sinus hypointense on T1 and hyperintense on T2. The patient underwent a left frontotemporal craniotomy with subtotal tumour resection followed by conventional fractionated radiotherapy (RT). Surgical histology identified a conventional chordoma. Due to tumour recurrence, the patient was submitted to proton beam therapy. Over the 4-year follow-up period no endocrine dysfunction was documented. 2) Female, 49-years-old, complained of diplopia, right eyelid ptosis and restriction of right eye abduction. A brain MRI showed a lesion adjacent to the right cavernous sinus. A right pterional craniotomy was performed and its histology revealed a chondroid chordoma. Six years later, a centimetric tumour residuum in posterior fossa cisterns was identified and proton beam therapy was performed. Endocrine dysfunction was not identified during the entire follow-up. 3) Female, 42-years-old, reported facial paralysis and hypoesthesia for several months. A cerebral MRI identified a clival lesion hypointense in T1 and hyperintense in T2. A transsphenoidal surgery was performed and the surgical histology identified a conventional chordoma. Due to a tumoral residuum, this patient was also submitted to proton beam therapy. Her endocrine evaluation did not identify any deficit, during the 3 years follow-up period. 4) Male, 45-years-old, reported headaches, diplopia and left sixth nerve palsy was observed. The brain MRI showed a clivus lesion that was submitted to transsphenoidal surgery and radiosurgery. It was identified a conventional chordoma. Two years later, he started with third, fourth and fifth nerves paralysis and a left spheno-cavernous and orbital apex recurrence was identified on MRI. A near-total tumoral resection was done. After that, he initiated polyuria, polydipsia and severe tiredness. His endocrine evaluation revealed insipidus diabetes, central hypothyroidism and central hypocortisolism.
Conclusions
We describe 4 cases of rare tumours with a follow-up ranging from 3 to 6 years. Despite the proximity of sella turcica, pituitary deficits were rare and were associated with tumour growth and aggressive behaviour. Nevertheless, follow up of pituitary function is recommended.

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P711

Prevalence and associated factors related to combined hypopituitarism in patients with congenital Growth Hormone deficiency

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Background and aim
Congenital Growth hormone deficiency (CGHD) may result from genetic or congenital disorders of pituitary development. It could be isolated or combined with other types of hypopituitarism. This study aims to evaluate the prevalence of combined hypopituitarism and its associated factors in patients with CGHD.
Patients and Methods
We conducted a retrospective study (1991-2019) at the Endocrinology department of Hedi Chaker University Hospital, Sfax, Tunisia. We involved 87 patients diagnosed with CGHD, whose clinical, biochemical, and imaging peculiarities were collected from medical charts.
Results
The mean age at diagnosis was 14 years (1-33 years), with a male predominance (59%). Seventy-five percent of cases were referred for short stature. We noted a delayed diagnosis in 65% of cases. The median height was 131 cm (67 - 169 cm). Severe growth delay was noticed in 38.6% of cases. The bone age was delayed in all cases comparing to chronological age. The average delay was of 48 months (6-152 months). Patients with isolated CGHD represented 20% compared to those with combined hypopituitarism (80%). Gonadotropic insufficiency was most often associated with GHD in 64%, followed by corticotropic and thyrotropic insufficiency in 48% and 38%, respectively. The prolactin axis was involved in 18%. The most characteristic profile of combined hypopituitarism implicated two or three axes in 25.9 % of each, four axes in 17.6 %, and all five pituitary axes in 10.6%. Associated factors related to the number of defective pituitary axes are displayed in table 1. Family occurance of hypothyouism is more frequent in patients featured as combined hypotuirism.
Discussion
Our work features a high prevalence of combined hypopituitarism in patients with CGHD of 80% vs 10% in the literature. These disparities could be partially explained by the pediatric age and the relatively short follow-up duration (<5 years) in the published studies. Otto *et al*. have shown the development of a second hormonal deficit in patients with isolated CGHD occurs on average 5.4 years after the initial diagnosis. In patients with CGHD, we recommend a regular evaluation of the remaining pituitary function to detect and treat delayed and subclinical forms of combined hypopituitarism.

Table 1:

Hypopituitarism	Isolated CGHD	2 axes	3 axes	4 axes	5 axes	P value
Consanguinity	46%	50%	68%	75%	100%	**0.001**
Familial cases	0%	15%	23%	40%	57%	**0.001**
Severe growth retardation	68%	66%	72%	86%	100%	**0.025**
Micopenis	0%	13%	18%	26%	33%	**0.001**

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P712

Successful management of severe hypoglycemia by octreotide LAR in an insulinoma patient

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Introduction
Surgical removal of the tumor is the primary treatment modality for insulinomas. However, in some patients, surgery is not possible. Octreotide, a somatostatin analogue, is known to suppress insulin secretion. However, there are little data on the use of octreotide in the treatment of insulinoma. Here, we present an insulinoma patient with severe clinical findings and successful control of hypoglycemia after long-acting octreotide.
Case
A 71-year-old male patient with hypertension was admitted to our clinic with long-standing hypoglycemia. He had frequent (1-2 times a day) neuroglycopenia symptoms, especially during fasting. He described that he detected glucose values below 40 mg/dl almost every day. Laboratory tests were as follows: fasting plasma glucose 23 mg/dl, insulin 34 mU/l, c-peptide 5 mg/l. Hospitalization was planned for further examination. At the 120th minute of the prolonged fasting test, capillary blood sugar was 39 mg/dl, plasma glucose was 33 mg/dl, insulin was 13.3 mU/l, c-peptide level was 3.1, and cortisol level was 14.5 mg/dl. Continuation of the test was not considered necessary, and 1 mg of glucagon was administered. Plasma glucose increased to 91 mg/dl at the 30th minute after glucagon. The patient, who was diagnosed with endogenous hyperinsulinism, was found to have negative insulin antibodies. Abdominal tomography revealed a 13x10 mm hypervascular lesion in the tail of the pancreas. The patient was diagnosed with insulinoma, and the operation was planned. He had episodes of severe hypoglycemia, and dextrose infusion was started. The patient was screened for multiple endocrine neoplasia, and no such finding was found. The importance of the operation was explained, however, the patient did not accept the surgical procedure. Under these circumstances, octreotide treatment was given at a dose of 3x50 mg for five days. Hypoglycemia did not recur, and dextrose infusion was interrupted. Monthly administration of octreotide LAR was planned, considering patient compliance. The patient who received octreotide LAR 10 mg and did not have hypoglycemia in the follow-up was discharged with the recommendation of frequent self-monitoring of blood glucose. His blood glucose monitoring at home ranged from 82 to 145 mg/dl. No hypoglycemia or complication was detected in the patient's subsequent outpatient follow-ups.
Conclusions
In patients with insulinoma who are unsuitable for surgery, long-acting octreotide formulation may be an effective therapy, even at low doses.

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Reproductive and Developmental Endocrinology

P170

RANKL signalling in female reproduction: a novel role of RANKL outside the skeleton?

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Background and Purpose
Infertility affects 15% of couples globally, and only few treatment options are available. Gonadotropins are classic and potent regulators of ovarian and female reproductive function, but novel endocrine crosstalk appears to exist between gonads and the skeleton that may influence female fertility. One of the new players include the RANKL signalling system, which consists of the receptor activator of nuclear factor κβ ligand (RANKL), the receptor RANK, and the decoy receptor osteoprotegerin (OPG). Recent studies suggest that the RANKL system is expressed in testis and is a novel regulator of germ cell proliferation and maturation. However, little is known about the role of the RANKL system in female gonads and whether it affects reproductive function, which is explored in the present study.
Methods
QPCR, immunohistochemistry and *in situ* hybridisation were performed to investigate the expression pattern of the RANKL system in mouse and human female reproductive organs. To explore the role of RANKL in ovaries, we utilised the Cre-loxP system to generate a granulosa cell-specific *Rankl* knockdown mouse model. The phenotype of the reproductive system was evaluated on sexually mature female mice. To extrapolate the data into the human setting RANKL and OPG were measured in serum and follicular fluid and associated with live birth rate after assisted reproductive techniques.
Results
The present study indicates that RANKL, RANK, and OPG are expressed in the female gonads. We validated that the *Amh* promotor can be exploited to achieve selective Cre recombinase activity in granulosa cells in female gonads. Pilot data indicate a higher pregnancy and birth rate in mice when RANKL is genetically suppressed in granulosa cells. In humans, we found that follicular fluid levels of RANKL and OPG are linked with number of stimulated follicles and live birth rate in women undergoing assisted reproductive techniques.
Conclusion
These preliminary findings suggest a role of RANKL in ovarian physiology and future investigations may untangle the exact role of RANKL for female reproductive function.

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P171

Chronic Unpredictable Stress (CUS) Induced Abnormal Sperm Morphology Associated with Male Reproductive Hormones and Phoenixin Expression in Male Rats

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Introduction
Chronic stress caused by prolonged emotional pressure may cause to multiple physiological problems including reproductive dysfunction. There is no doubt that infertility can cause chronic stress. However, the effect of chronic stress-induced reproductive dysfunction is still debatable. Thus, this study aims to demonstrate CUS effect on reproductive system.
Methodology
Sprague Dawley (SD) rats ($n=16$) were divided into two groups: i) non-stress control group ii) CUS-induced group. The CUS consists of different stressors that were induced for 28 days, and each group was subjected to behavioural tests. To identify the effect of CUS at the hypothalamic level, gene expression study was done to determine the expression of stress and reproductive neuropeptides. As hypothalamic neuropeptides responsible to regulate hormone circulation, ELISA test was done to measure the plasma stress and reproductive hormones concentration. To identify the effect of CUS on the peripheral level, histopathologic evaluation of the rats' testis was done with H& E staining. The seminal fluid was analysed for sperm count and morphological changes.
Results
The stress model was confirmed by the sucrose-preference and force-swimming test. Hypothalamically, the expression of *corticotropin-releasing hormones* (*CRH*) in CUS-induced rats increased significantly compared to control group ($P<0.05$). The upregulated CRH was supported by the elevation of plasma cortisol in CUS-induced rats ($P<0.05$). The effect of CUS also downregulated *phoenixin* (*PNX*) expression in the hypothalamus of CUS-induced rats by 0.5 fold lower than the control group ($P<0.05$). However, *kisspeptin*, *spexin* (*SPX*) and *gonadotropin-inhibitory hormone* (*GnIH*) showed no difference between the two groups. The primary regulator of reproductive system, *gonadotropin-stimulating hormone* (*GnRH*) expressed significantly higher than control ($P<0.05$). Despite the increased expression of *GnRH*, plasma LH and testosterone concentration were significantly low ($P<0.05$) in CUS-induced rats compared to control group. The effect of CUS demonstrated anomalous testis morphology of CUS-induced rats consisting of abnormal architecture with visible interstitial spaces between seminiferous tubules and the absence of spermatogenesis. The reproductive deficit of CUS-induced rats was further demonstrated with an increase of 20% in abnormal sperm count compared to only 3% in control group ($P<0.0001$).
Conclusions
Our CUS model of chronic stress demonstrated a correlation with reproductive function where chronic stress caused low concentration of reproductive hormones, high abnormal sperm count and abnormal testis morphology. These findings interestingly suggest the correlation with low phoenixin expression as reproductive system regulator.

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P172

Ketoacidosis in Type 1 Diabetics: Epidemiological and Clinico-Biological Profile: About 423 Patients

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Introduction
Diabetic ketoacidosis (DKA) is a serious metabolic complication of diabetes with an annual incidence between 4.6 and 8 episodes per 1000 diabetic patients, it is responsible for a considerable socio-economic impact, however its mortality remains low.
Objectives
The objective of the study is to clarify the epidemiological and clinico-biological profile of type 1 diabetic patients hospitalized and followed for diabetic ketoacidosis.
Materials and Methods
Retrospective descriptive study about 423 type 1 diabetic patients hospitalized in the department of endocrinology and metabolic diseases followed for diabetic ketoacidosis between 2012 and 2022.
Results
The average seniority of diabetes was 6.7 years, inaugural ketoacidosis was recorded in 89 cases. All the patients had stayed in intensive care for an average of 2.1 days. The mean HbA1c was 10.9 $\pm$ 0.8%. The most common decompensation factors were infection in 50.6%, discontinuation of insulin therapy in 24.8% and a combined cause in 24.6%. Our patients were not aware of the vital necessity of insulin in 43.9% of the cases.
Conclusions
Despite recent progress in the management of type 1 diabetes, ketoacidosis is still common in some young patients, in chronic imbalance, new to therapeutic education. Good education and personalized support are essential to prevent and reduce the incidence of this severe metabolic complication and thus limit its socio-economic cost.

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P173

Iodine deficiency in pregnancy reflected by ioduria and mother-child pairs thyroid status

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Background
Iodine deficiency disorders are a global health problem partially eliminated by salt iodization national programmes. In Poland, this micronutrient shortage diminished over the last two decades, however in some particularly vulnerable groups like pregnant and breastfeeding women additional supplementation of iodine is beneficial for both mother and newborn. The programme's effectiveness should be regularly evaluated. The matter of concern remains the optimal recommendation of additional iodine intake in hypothyroid women.
Objectives
The study aimed to evaluate the adherence of pregnant females to recommendations and iodine intake impact on thyroid parameters of both – mothers and their newborns.
Methods
Healthy and euthyroid levothyroxine-treated women in 3rd trimester of a pregnancy before delivery ($n=91$) and their newborns ($n=101$) were recruited to the study. The questionnaire concerning iodine supplementation was performed. Thyroid hormones analyses (TSH, ft3, ft4, a-TPO, a-Tg) measured by ECLIA were performed in mothers and cord blood of newborns, with additional assessment of screening thyrotropin (TSHs) from heel prick at the 3rd-4th day of life. Ioduria was assessed by maternal urinary iodine concentration (UIC), corrected by urine creatinine (ELISA) as UIC/crea ratio from a single urine sample by HPLC-UV method. This research was funded by National Science Centre in Poland (2019/33/N/NZ5/02303) as PRELUDIUM-17 grant.
Results
Supplementation of iodine was declared by 68% of women. The recruited cohort of females had median UIC (IQR) 106 (69 - 156) µg/l and UIC/crea ratio was 104 (62 - 221) µg/g, revealing iodine deficiency (according to WHO criteria UIC or UIC/crea <150). Additionally, almost 20% had UIC/crea as low as <50 µg/g. No significant difference in median UIC (IQR) was observed in patients supplemented (105 µg/l, 69-170) and non-supplemented iodine (99 µg/l, 84-130; $P=0.55$). Optimal UIC/crea was reflected by the lowest TSH ($P=0.02$) and a-TPO ($P=0.02$) in mothers. TSHs above 5 mIU/l was seen in 6% of newborns.
Conclusions
The presented group of pregnant women was iodine deficient in terms of ioduria and TSHs due to WHO/UNICEF criteria. Almost one-third of women did not follow the recommendation to supplement I during pregnancy. Nevertheless, in women who declared I intake, the supplementation seemed ineffective. A sufficient iodine supply may improve the thyroid parameters of mother and newborn.

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P174

Congenital Adrenal Hyperplasia – When does Gender Identity Begin?

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Introduction
Congenital adrenal hyperplasia (CAH) is a genetic condition which impairs enzymatic steroidogenesis of the adrenal cortex, leading to excessive androgen production. CAH phenotype is heterogeneous. In the mildest forms, it can present with hirsutism, acne and menstrual irregularities. Problems related to gender identification arise in about 5% of people with CAH with a 46,XX karyotype.
Objective
We present the case of a young female-to-male (FtM) transgender, who was diagnosed with non-classical CAH during medical evaluation prior to the initiating of hormone therapy.
Clinical Case
We present the case of a 23 year old youth, who was born from a twin pregnancy, with female gender assigned at birth. Since early, this child identified with the opposite sex – he would mostly play with boys and dressed up to look like one of them. Their parents report that as soon as 4 years of age, he would already tell he was a boy. Menarche occurred at teh age of 15, with irregular menstrual cycles and dysmenorrhea. He reports hirsutism since adolescence. At 17 years of age, he sought medical evaluation, as he was determined to go through a sexual reassignment process. The initial biochemichal evaluation showed an increase in basal plasma 17-hydroxyprogesterone (17-OHP) (9.75 ng/ml), increased 17-OHP in the cosyntropin stimulation test (0 min: 9.48 ng/ml, 60 min: 20.31 ng/ml) and normal dehydroepiandrosterone (199 mg/dl (35-430)). There results suggested the diagnosis of non-classical CAH. The karyotype revealed a 46, XX pattern. When he as 19 years old, he was started on hormone therapy with testosterone and underwent bilateral mastectomy. He is currently awaiting the remaining gender-affirming surgical procedures – he intends to undergo phalloplasty, hysterectomy and adnexectomy.
Conclusions
Non-classical CAH may be associated with atypical sexual development and, occasionally, with changes in gender identity, as in the presente case. Sexual development seems to be influenced by the exposure to androgens, which occurs since intrauterine life. This argument is supported by the masculinizing effects of androgen exposure in children with 46,XX karyotype, which may determine their behaviours, sexual orientation and gender identity. This issue becomes particularly relevant given the preference for early feminization in clinical practice in these individuals. Indeed, there is no evidence that this early gender definition approach is associated with better quality of life and sexual function. The approach to transgender individuals should be multidisciplinary and concomitant anomalies of sexual development, such as CAH, must be investigated.

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P175

Women with preeclampsia show altered cortico- and sex steroid profiles

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Background
Preeclampsia (PE) is a complex condition of pregnancy, associated with substantial perinatal morbidity and mortality, affecting 2% to 8% of pregnancies worldwide. Its hallmarks are high blood pressure (hypertension) and endothelial dysfunction, leading to potential end-organ injury. Affected organ systems include liver, blood, kidneys, brain and placenta. In the present study, we investigated steroid hormones such as progestagens, estrogens, androgens, and glucocorticoids during pregnancy in order to describe maternal and fetal development. Aim of the present study was to compare steroid hormonal profiles throughout pregnancy between pregnant women, who develop preeclampsia and normotensive pregnant women.
Methods
Serum levels of 15 steroids were measured in 14 pregnant women with preeclampsia and 36 normotensive pregnant women by isotope-dilution liquid chromatography tandem mass spectrometry (ID-LC-MS/MS) at 8 different time points throughout pregnancy (12, 20, 24, 28, 32, 36 weeks of gestational age) as well as at delivery and 24h postpartum.
Results
Pregnant women with PE showed significantly higher mean levels of dehydroepiandrosterone (DHEA; $P \leq 0.001$), dehydroepiandrosterone sulfate (DHEAS; $P \leq 0.001$), testosterone ($P \leq 0.001$) as well as androstenedione ($P \leq 0.001$) and significantly lower mean levels of the cortisol/cortison ratio ($P = 0.001$), 11-deoxycortisol ($P = 0.001$), dihydrotestosterone ($P \leq 0.001$) and estradiol ($P = 0.024$ throughout pregnancy compared to healthy controls.
Conclusion
PE status significantly altered serum steroid levels compared to normotensive pregnant women throughout pregnancy. A comparison of substrate-product ratios between women with PE and normotensive pregnant women may serve to derive new indices and candidate genes for steroid-metabolizing enzymes that should be further investigated as potential biomarkers for the prediction of PE.

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P176

Machine learning algorithm for predicting polycystic ovary syndrome based on voice samples

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Introduction
Several investigations proved the presence of receptors for androgens, estrogens and progesterone in vocal folds. The most common endocrine disorder causing alterations in the aforementioned hormones concentrations is polycystic ovary syndrome (PCOS), which, according to several studies, can cause voice changes, especially deepening of its timbre. Over last few years, vocal changes accompanying many different disorders have been a subject of research with the use of machine learning (ML) - an algorithm-centered branch of artificial intelligence.
Aim
The aim of this work was the voice analysis in PCOS and its subgroup - PCOS with laboratory hyperandrogenism (PCOS-HA). The analysis of voice samples comprised evaluation of chosen acoustic features in terms of their ability to predict selected groups, as well as training the classifiers evaluating the probability of a given voice sample's owner belonging to PCOS or PCOS-HA.
Materials and Methods
The first study group comprised 39 patients with PCOS, while control group included 56 healthy women. The PCOS-HA subgroup comprised 17 patients and 49 healthy women as a control group. All participants underwent anthropometric measurements, oral glucose tolerance test, hormonal profile assessment and transvaginal ovarian ultrasonography. All participants provided voice recordings, further submitted for analysis by ml.
Results
The acoustic analysis revealed the differences between study groups and their healthy counterparts in terms of several dozen of acoustic features. Two of them were associated with PCOS independently of age, free androgen index and fasting glucose concentration. The classifier evaluating the probability that the voice analysis of the recorded woman indicates her belongingness to the PCOS group was distinguished by the balanced accuracy equal to 74.4%, the sensitivity of 57.1%, the specificity of 91.7%, the precision of 80% and the area under the curve (AUC) of 0.810. Five acoustic features were associated with PCOS-HA independently of age, BMI and fasting glucose concentration. The classifier evaluating the probability that the recorded woman belongs to the PCOS-HA group was distinguished by the balanced accuracy equal to 85%, the sensitivity of 100%, the specificity of 70%, the precision of 57.1% and the AUC of 0.950.
Conclusions
PCOS and PCOS-HA influence vocal changes. The classifiers predicting the probability of PCOS, based on the voice analysis, do not fulfil the criteria of a useful screening test in case of no additional information about the recorded patient. The classifier predicting the probability of PCOS-HA, based on voice analysis, fulfils the criteria of a useful screening test.

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P177

Hyperandrogenism-related metabolic changes in drug-naive transmen compared to cisgender women: A case-controlled study

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Introduction
The etiology of gender dysphoria is still unclear. Although prior studies have shown trans men have higher androgen levels than cisgender women, they all concluded unselected populations. Our purpose to perform this study is to evaluate transmen's hormone profile and metabolic status to compare cisgender women in a more selected population. This is the first case-controlled study to compare anthropometric, metabolic, and endocrinological parameters of drug-naïve transmen with those of cisgender women.
Methods
We designed this study as a single-center observational cohort study. We included 70 drug-naive transmen, and the control group comprised 34 healthy cisgender women. We measured and compared hormone profiles and metabolic parameters in the two groups.
Results
Of the 70 transmen individuals, 16 (22.85%) met Rotterdam criteria and were diagnosed with polycystic ovary syndrome (PCOS), 4 individuals in the control

Table 1 Comparison of the parameters after patients with polycystic ovary syndrome excluded

	Transmen($n=54$)	Ciswomen($n=30$)	p
Age(Years)	25.09±5.02	26.86±3.81	0.044
BMI	22.88±3.48	23.71±5.39	0.863
Waist circumference(cm)	77.87±9.56	73.21±11.12	**0.009**
F-G Score	3.15±2.28	3.76±2.52	0.341
Fasting glucose(mg/dl)	83.77±7.41	82.44±7.37	0.477
Triglyceride(mg/dl)	86.75±66.40	57.86±19.81	**0.002**
Total cholesterol(mg/dl)	171.53±31.56	176.70±19.26	0.436
LDL(mg/dl)	104.30±25.01	105.30±18.10	0.595
HDL(mg/dl)	53.07±8.56	59.83±11.06	**0.005**
IGF-1(μg/l)	188.30±57.09	161.55±49.84	**0.024**
FSH(U/l)	7.73±2.33	7.40±2.20	0.881
LH(U/l)	6.03±2.16	6.25±2.36	0.798
Estradiol(ng/l)	48.39±18.11	58.21±35.15	0.132
Total testosterone(μg/l)	0.59±0.28	0.43±0.18	**0.004**
SHBG(nmol/l)	58.27±22.32	67.03±29.88	0.227
FAI	1.25±0.97	0.81±0.44	**0.032**
Androstenedione(μg/l)	4.02±5.91	2.40±0.87	**0.012**
DHEAS(μg/l)	268.98±113.95	202.81±72.10	**0.008**
Prolactin(μg/l)	17.48±9.90	19.43±10.38	0.384
17-OH progesterone(μg/l)	1.25±0.66	0.81±0.33	**0.005**
HsCRP(mg/l)	1.88±1.87	1.73±2.02	0.465
Mean muscle strength	26.37±4.37	24.51±3.96	0.087
HOMA-IR	2.14±0.90	1.80±1.48	**0.011**
HOMA-β	180.52±85.80	159.39±99.88	0.124
AUC(Glucose)	203.61±39.68	197.59±51.47	0.571
AUC(Insulin)	94.75±47.75	87.14±86.54	**0.032**

LDL:Low Density Lipoprotein, HDL:High Density Lipoprotein, IGF-1:Insulin Like Growth Factor, SHBG: Sex Hormone Binding Globuline, FAI:Free Androgen Index, DHEAS:Dihidroepiandrosetenedione Sulfate, HsCRP:High Sensitive-C Reactive Protein, HOMA-IR:Homeostatic Model Assessment for Insulin Resistance, AUC:Area Under the Curve

group met the criteria (11.7%). Although we matched body mass index in the groups, total testosterone, free androgen index, androstenedione, 17-hydroxy-progesterone, muscle strength, triglyceride, and homeostatic model assessment of insulin resistance levels were significantly higher in the trans men than in the cisgender women ($P<0.05$). Even after were excluded PCOS patients, hyperandrogenemia was apparent in the transmen.
Conclusions
Our study showed that transmen have clearly higher androgen levels, which may have been the reason for metabolic changes compared to cisgender women. But the main reason for hyperandrogenism in drug-naïve transmen is still not known, and more comprehensive studies are needed.

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P178

Are there Differences Between Androgens When Studying Androgenisation in the Transgender Patient?

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Introduction
In gender affirming therapy of the transgender male, increasing doses of testosterone are administered and as the androgen dose increases, various biochemical parameters such as haematocrit, creatinine and PSA increase. It is not known whether any parameters have advantages in monitoring this androgenisation. Our study evaluates the correlation between the increase in androstanediol glucuronide, testosterone, free testosterone and free androgen index (FAI) with the aforementioned biochemical parameters in a cohort of 20 trans men who started gender affirming therapy.
Material and Methods
Samples were obtained from 20 transgender men at the initiation of testosterone cypionate therapy and after each 3-monthly dose increment of 25 mgrs, up to a maximum of 250 mgsr during one year of treatment. Testosterone, free testosterone, DHEAS, on the Snibe Maglumi platform, PSA and creatinine on the Siemens atellica autoanalyser and haematocrit on the Beckman Coulter DXH900 analyser were analysed. The 3α androstanediol glucuronide (3αAG) was analysed by ELISA (DRG). Correlations were performed with Sperman's test between the different parameters using SPSS 25.0 statistical software.
Results
For haematocrit all androgens analysed were significantly correlated, however there are differences in the Rho (ρ) between each pair. FAI has the best correlation:ρFAI= 0.568/$P<0.001$. The correlation coefficients of the other androgens were:ρtestosterone= 0.556,ρfTestosterone= 0.545,ρ3αAG = 0.535,ρDHEAS= 0.532 with a $P<0.001$ for all of them. Serum creatinine levels correlate only with androstenedioneρandrostenedione=0.373/$P=0.002$, and DHEASρDHEAS=0.297/$P=0.010$. This correlation decreases in oophorectomised patients. For PSA, as for haematocrit, all androgens were significant. The best correlation was for testosteroneρTestosterone= 0.347/$P=0.003$ followed by free testosterone:ρfTestosterone= 0.274/$P=0.021$. The other androgens showed no significant correlation, although FAI ($P=0.088$) and androstenedione ($P=0.078$) showed a clear trend towards a significant correlation.
Conclusions
The different androgens have different correlation coefficients depending on the marker used. FAI obtained the best result with haematocrit, making it the parameter of choice when assessing the relationship between a given dose and its increase. Significance was obtained for creatinine with androstenedione and DHEAS and for PSA with testosterone and free testosterone. The different androgens are associated with different biochemical parameters and should therefore be assessed individually when evaluating androgenisation in these subjects.

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P179

Characteristics of dilated aortas in patients with Turner syndrome: clinical, histological and cytogenetic analysis

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Turner syndrome (TS) is a rare condition with a high frequency of aortic dilatation (AD) and a risk of aortic dissection. Our objective was to evaluate the characteristics of the aorta in patients with TS.
Methods
Analyses of aortic walls were obtained during prophylactic aortic replacement. Histological description and measurement of a standardized media degenerative score (MDC) were performed. Cytogenetic analysis quantified the level of monosomy X in blood karyotype, buccal smear and aortic media by FISH technique.
Results
Eleven patients aged 39 years (median; IQR: 29.5-46.5) with a mean aortic index of 29 mm/m^2 (IQR: 26.7-30.1) were enrolled. Ten had a bicuspid aortic valve (BAV). Blood karyotypes showed 45,X; 45,X/46,XX and an abnormal X chromosome in 7/11, 1/11, and 3/11 cases, respectively. Degenerative elements were present in all aortas, with an MDC score=9.0 (IQR: 7-10.5). Aortic monosomy was correlated with that of the blood karyotype ($P=0.003$). However, one patient with 5% of 45,X mosaicism in blood cells had a 70% X monosomy in her aortic media. To our knowledge, this is the first systematic histological analysis showing early degenerative aortic characteristics in young women with ST. Our study shows that a low level of monosomy 45,X in the blood is not necessarily reassuring regarding a potential risk of aortic dilatation and therefore dissection.

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P180

Vitamin D and IVF/ICSI outcome: Are we measuring the right metabolites?

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Background
Numerous studies have suggested that optimal vitamin D status increases treatment success of women undergoing assisted reproductive treatments. However, conflicting data exist, and the relationship remains controversial, prompting the need for more comprehensive studies investigating all the metabolites of vitamin D in women undergoing IVF/ICSI treatment.
Objective
To investigate the relationship between follicular fluid levels of the three main vitamin D metabolites 25OHD$_3$, 24,25(OH)$_2$D$_3$ and 1,25(OH)$_2$D$_3$ and IVF/ICSI treatment outcome.
Study design
Follicular fluid and serum samples from 116 women undergoing IVF/ICSI treatment were analyzed. Expression of the vitamin D regulating enzymes (CYP2R1, CYP27B1, CYP24A1) and the vitamin D receptor (VDR) was investigated in human ovaries.

Results
The vitamin D regulating enzymes CYP2R1, CYP27B1, CYP24A1 and VDR were expressed in the human ovary, enabling the follicles to activate, inactivate and respond to vitamin D metabolites. Moreover, all three investigated vitamin D metabolites $25OHD_3$, $24,25(OH)_2D_3$ and $1,25(OH)_2D_3$ were present in follicular fluid and in serum. 25OHD levels were similar in serum and follicular fluid, while levels of $24,25(OH)_2D_3$ were higher and $1,25(OH)_2D_3$ lower in follicular fluid than in serum. Upon stratifying women according to live birth outcome, women achieving a live birth had significantly higher follicular fluid levels of the $24,25(OH)_2D_3$ metabolite (17.4 $\pm$ 8.5 vs 13.5 $\pm$ 6.3 nmol/l, $P=0.015$) and a higher $24,25(OH)_2D_3/25OHD_3$ ratio (0.25 $\pm$ 0.07 vs 0.21 $\pm$ 0.07, $P=0.029$) compared to women with an unsuccessful cycle. Also, when grouping women in intervals according to their follicular fluid $24,25(OH)_2D_3/25OHD_3$ ratio the live birth rate significantly increased across increasing ratio intervals (15%, 20% and 50% for the <0.2, 0.2-0.3 and >0.3 group, respectively, $P=0.019$).
Conclusions
This study reveals that a higher follicular fluid $24,25(OH)_2D_3$ level and $24,25(OH)_2D_3/25OHD_3$ ratio is associated with increased live birth rate in women undergoing IVF/ICSI treatment.

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P181

In Vitro Fertilization in Polycystic Ovary Syndrome: Treatment Individualization Based on Genetic Singularities

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Introduction
Polycystic ovary syndrome (PCOS) is one of the most common causes of anovulatory infertility. Polymorphisms in genes related to follicular recruitment and development, such as the follicle-stimulating hormone receptor (FSHR) and the oestrogen receptor 1 (ESR1) genes, and their impact on biochemical phenotype and response to controlled ovarian stimulation in women with PCOS have been studied in different populations, with inconsistent results.
Aims
To evaluate the influence of FSHR rs6166, p.Asn680Ser (c.2039A>G) and of ESR1 rs2234693 (Pvull c.453-397 T>>>C) polymorphisms on biochemical phenotype and response to controlled ovarian stimulation in women with PCOS and infertility.
Materials and methods
Retrospective observational study of women with a diagnosis of PCOS (by Rotterdam criteria) and infertility, who underwent *in vitro* fertilization (IVF). A short GnRH antagonist protocol was used for controlled ovarian stimulation. Genotyping of the FSHR rs6166 and of the ESR1 rs2234693 polymorphisms was performed and hormone levels and IVF results were compared between different genotypes.
Results
80 women with PCOS and infertility were evaluated, with median age of 33.1 $\pm$ 3.6 years and mean body mass index of 26.8 $\pm$ 5.4 kg/m^2. The genotype distribution of FSHR rs6166 polymorphism was 32.5% AA, 48.8% AS and 18.8% SS, and of ESR1 rs2234693 polymorphism was 21.5% CC, 46.8% CT and 31.3% TT. Women with the SS variant of the FSHR rs6166 polymorphism had higher FSH levels on the third day of the menstrual cycle (9.6 $\pm$ 9.8 vs 6.52 $\pm$ 1.6 [AA] and 5.5 $\pm$ 1.6 [AS] UI/ml, $P=0.006$), with no differences in other baseline hormonal parameters (LH, oestradiol, progesterone, testosterone and anti-mullerian hormone) or in antral follicle count between genotypes. Additionally, women with the SS variant of the FSHR polymorphism required higher cumulative doses of FSH for controlled ovarian stimulation (1860.5 $\pm$ 627.8 vs 1498.1 $\pm$ 359.3 [AA] and 1425.4 $\pm$ 474.8 [SA] UI, $P=0.046$), but showed no difference in response (follicle count on the day of ovulation induction, number of oocytes and number of blastocysts obtained). Women with different ESR1 genotypes showed no differences on baseline hormonal parameters or response to controlled ovarian stimulation.
Conclusions
The SS variant of the FSHR rs6166 polymorphism was associated with higher baseline FSH levels and higher cumulative doses of FSH in controlled ovarian stimulation, which may suggest a lower sensitivity to FSH. Thus, controlled ovarian stimulation with higher doses of FSH may be more appropriate in women with this genotype. The ESR1 rs2234693 polymorphism was not associated with differences in biochemical phenotype or response to ovarian stimulation.

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P182

Sublingual estradiol only, offers no apparent advantage over combined oral estradiol and cyproterone acetate, for Gender Affirming Hormone Therapy (GAHT) of treatment-naïve transwomen: Results of a prospective pilot study

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Background
The standard approach for Gender-Affirming Hormone Therapy (GAHT) of transgender women (TW) in Israel is oral estradiol (OE) combined with the potent anti-androgen cyproterone acetate (CA). Recently, many of our non-binary patients have requested sublingual estradiol (SLE) without CA, under the unproven belief it preserves erectile function, and does not induce depression. Preliminary data in a few subjects, who self-practiced this approach, suggested it also maintained higher testosterone levels.
Hypothesis
By not suppressing testosterone (T) as profoundly, SLE should be less detrimental to sexual function, and might be superior to OE for improving dysphoria.
Study design
A 6 months controlled, unblinded and non-randomized, prospective study of treatment-naïve TW seeking GAHT.
Patients and Methods
22 healthy, treatment-naive TW. The SLE arm consisted of 0.5 mg of estradiol 4 times a day, while the OE consisted of oral 2 mg estradiol together with 10 mg CA once daily. Subjects underwent exhaustive chemical, hematologic and hormonal laboratory assessments, and body composition analysis at baseline and after 6 months. Furthermore, they completed validated dysphoria, sexual desire and function questionnaires.
Results
At baseline, the only difference between the groups was age. Subjects who chose SLE, were older 26.3 $\pm$ 5.8, vs. 20.1 $\pm$ 2.3 yr for OE ($P=0.006$). Baseline testosterone 19.5 $\pm$ 6.8 nmol/l; estradiol 113.3 $\pm$ 32.7 pmol/l; LH 4.3 $\pm$ 1.4 IU/l; FSH 4.5 $\pm$ 3.4 IU/l; and prolactin 226 $\pm$ 150 mIU/l were identical between the groups. By paired comparisons, GAHT generated significant, and expected changes at 6 months in both groups: creatinine, hemoglobin, hematocrit, total and LDL cholesterol, testosterone, gonadotropins all decreased, while estradiol and prolactin rose. BMI remained unchanged, but there was a significant increase in fat mass, and a decrease in lean body mass in both groups. At 6 months, the only differences between the treatment groups were higher estradiol, and LH in the SLE group: 204.6 $\pm$ 63.3 vs. 109.7 $\pm$ 53 pmol/l, $P=0.02$; and 3.5 $\pm$ 1.2 vs. 1.6 $\pm$ 1.3 IU/l, $P=0.007$, respectively. Median estradiol, 90 minutes after 0.5 mg SLE was 1721 [IQR 1000-2432] pmol/l. Remarkably, dysphoria did not improve in either group during the study period. Sexual desire and function decreased significantly with both treatments, and were not spared by the SLE protocol.
Conclusions
GAHT of TW with SLE over 6 months, offers no clear advantage over the standard OE approach that includes CA, neither in hormonal, biochemical and body composition variables, while it generates recurring supraphysiological estradiol concentrations throughout the day, the safety of which, particularly with respect to thrombogenicity, remains to be determined.

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P183

Misdiagnosis of 46, XY DSD in a childhood Bone Marrow Transplantation survivor

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Introduction
Endocrine late effects can manifest in hemopoietic stem cell transplantation survivors who were exposed to myelosuppressive conditioning treatment. These include dysfunction of the hypothalamic/pituitary, thyroid, and gonads leading to

premature ovarian insufficiency and primary amenorrhoea. In addition, metabolic dysregulation and increased risk of diabetes have been observed in these patients. The investigation for primary amenorrhoea in this condition can rarely be complicated by an abnormal karyotype of 46XY in females who received HSCT from male donors leading to a misdiagnosis of disorder of sex development (DSD). To the best of our knowledge, only a handful of cases of misdiagnosed 46, XY DSD following bone marrow transplantation have been reported worldwide.
Case history
A 17-year-old female was referred to our endocrine clinic for the management of primary amenorrhoea as she was newly relocated to the UK. She was diagnosed with Beta Thalassemia Intermedia at age of 2 and had allogeneic hemopoietic stem cell transplantation from her brother at age of 2.5 with complete recovery. She had chemotherapy including Cyclophosphamide and Busulfan for myelosuppression in preparation for HSCT. Later, she consulted an endocrinologist abroad at the age of 16 due to delayed puberty. Her blood test showed a picture of hypergonadotrophic hypogonadism. Further investigations revealed a hypoplastic uterus. Genetic studies performed on a peripheral blood lymphocyte showed karyotype of 46XY which led to the suspicion of DSD. This usually necessitates surgical removal of gonads due to the risk of gonadoblastoma. However, as the clinical manifestations were not entirely consistent with the diagnosis given the presence of gonads and some secondary sexual characteristics, the diagnosis was revisited. A repeat chromosomal analysis on skin fibroblasts was arranged this time and demonstrated a karyotype of 46XX. This led to a diagnosis of premature ovarian insufficiency likely due to childhood chemotherapy. She was started on conjugate oestrogen and achieved pubertal changes in line with Tanner stage III. The oestrogen dose was incrementally built up, and her sexual development improved to Tanner stage IV. Her repeat ultrasound pelvis in Dec 2022 showed a small left ovary and an unidentified right ovary with a normal uterus.
Conclusion
Chromosomal analysis could be misleading following gender mismatched bone marrow transplant. This can lead that the patient to undergo unnecessary and potentially life changing invasive procedures. Pre- and post-treatment chromosomal analysis is essential in such cases.

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P184

Human muscle fibers in previous users of anabolic steroids display persistent increased myonuclei number years after cessation

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Background and Objective
Information on the long-term effects of anabolic androgenic steroids (AAS) use on the myocellular properties of human skeletal muscle is scarce, despite being the primary target of AAS. Animal studies suggest persistence of upregulated myonuclei numbers following AAS discontinuation. Few human studies have investigated the effects of AAS on human skeletal muscle cell morphology and exclusively focused on current AAS users. No data exist elucidating the long-term effect on human skeletal myofiber properties in previous AAS users. The objective of this study was to investigate the effects of AAS use on myofiber morphology and myonuclei content in current and former AAS users.
Methods
Community-based cross-sectional study including men involved in recreational strength training. Biopsies were obtained from the quadriceps muscle (*vastus lateralis*). Immunofluorescence analysis was performed to quantify myofiber size (CSA) and myonuclei numbers. AAS usage was evaluated using standardized questionnaires.
Results
We included a total of 25 participants: 8 current and 7 previous AAS users and 10 controls with no prior AAS use. Mean (SD) age was 31 (7) years and did not differ between groups. Median (25^{th}-75^{th} percentiles) accumulated duration of AAS intake was 174 (101 – 206) and 140 (24 – 260) weeks in current and former AAS users, respectively ($P=0.482$). Mean (95% CI) elapsed duration since AAS cessation was 4.0 (1.2; 12.7) years among former AAS users. Type II muscle fibers in former AAS users displayed smaller myonuclear domains than controls ($P=0.013$), corresponding to a higher myonuclei-cytoplasma ratio. Further, the ratio of perimeter per myonuclei in type II fibers tended to be lower in former users than controls ($P=0.060$). Type I fibers in current AAS users exhibited increased amounts of satellite cells per myofiber ($P=0.031$) and more myonuclei per myofiber ($P=0.043$) compared with controls.
Conclusions
AAS use is associated with increases in satellite cell and myonuclei content. Elevated myonuclei content was observed in type II fibers obtained from previous AAS users with a mean of 4 years after AAS cessation. Thus, AAS usage may lead to superior re-training ability ('muscle memory') years after AAS cessation. The findings enhance our understanding of the long-term effects of supraphysiological AAS intake on human skeletal muscle mass.

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P185

Fear of Hypoglycemia in Parents of Young Type 1 Diabetic Patients and Impact on Glycemic Control

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Introduction
Hypoglycemia is the most frequent iatrogenic acute complication in type 1 diabetics, it is a potentially serious complication, which can lead to coma. Many advances in new generation insulins, self-monitoring methods and therapeutic education have reduced the incidence of this complication. Nevertheless, hypoglycemia still generates great fear and anxiety in parents of young type 1 diabetic patients, which can be accompanied by several therapeutic errors.
Objectives
To describe the fear of hypoglycemia in parents of young T1D patients as well as the resulting therapeutic errors and the impact on glycemic control.
Materials and Methods
Cross-sectional descriptive study carried out in the endocrinology and metabolic diseases department, including the parents of young T1D patients aged between 15 and 20, hospitalized in the departments or received in transition consultation during the year 2022. Our study excluded severe hypoglycaemia.
Results
Our study included 92 parents of young T1D patients aged on average 17.1 years, the mother was the most involved in the management of diabetes in 75%, and the father in 25%. It was noted a fear of hypoglycemia in all parents but mainly nocturnal in 89%. In cases of mild to moderate hypoglycemia, 90% of parents advised a double consumption of the carbohydrates necessary for resugar, a snack was taken in 45%, the next insulin dose was generally reduced in 50% of cases, not taken in 5%, the average HBA1C was 9.4%.
Conclusions
Hypoglycemia is a frequent complication, a source of anxiety for patients and their families requiring targeted education of patients but also of parents and siblings. Education should be a flexible process, adapted to the specific and changing needs of young people and their families, as they go through the different stages of their lives.

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Gene expression differences between small and large follicles

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In assisted reproduction, poor ovarian response to controlled ovarian stimulation (COS) leads to poor oocyte yield and depends on the genetic background. We compared the expression of key-genes, coding proteins regulating follicular development, between small (<10 mm) and large ovarian follicles (>16 mm), assuming the size as a hallmark of follicle maturation and oocyte fate. Twenty-

two patients undergoing COS were enrolled in a fertility clinics. Granulosa cells and follicular fluids (FFs) were grouped according to size of ovarian follicles (small follicles, 'SFs', diameter <10 mm, $n=22$; large follicles, diameter, 'LFs', >16 mm, $n=22$) and collection in the antral or luteal stage. Gene expression was analyzed by digital droplet PCR, while testosterone (T) and estradiol (E_2) levels were measured by homogeneous time-resolved fluorescence. Results were matched with clinical data by principal component analysis (PCA). Ethics Committee approval was obtained, and statistical analysis was performed using Mann-Whitney's U-test ($P<0.05$; means$\pm$SEM). *FSHR* and *GPER* gene expression was higher in SFs than LFs, supporting their role in promoting follicular dominance via activation of proliferative signals ($P<0.05$; *FSHR*-LFs: $1x10^{-3}\pm0.1x10^{-3}$ fold/housekeeping gene expression; *FSHR*-SFs: $4.6x10^{-3}\pm1.1x10^{-3}$; *GPER*-LFs: $2.8x10^{-3}\pm0.3x10^{-3}$; *GPER*-SFs: $7.8x10^{-3}\pm1.7x10^{-3}$). *FSHR/GPER* gene expression ratio resulted to be lower in LFs than SFs, indicating the potential to counteract apoptotic signals linked to FSHR overexpression ($P<0.0001$; *FSHR/GPER*-SFs: 1.065 ± 0.3 fold/housekeeping gene expression ratio; *FSHR/GPER*-LFs: 0.37 ± 0.052). Marked *CCND2* and *AMHR2* expression were found in SFs as well, indicating cell proliferation ($P<0.05$; *CCND2*-LFs: $0.1\pm8x10^{-3}$ fold/housekeeping gene expression; *CCND2*-SFs: $0.15\pm18x10^{-3}$; *AMHRII*-LFs: $5x10^{-3}\pm0.8x10^{-3}$; *AMHRII*-SFs: $8x10^{-3}\pm1.3x10^{-3}$). No different *CYP19A1*, *LHCGR*, *XIAP* and *TP53* gene expression was found between SFs and LFs ($P\geq0.05$). In FFs, higher T levels were detected in LFs *vs* SFs ($P<0.05$; SFs: $1.7x10^{-9}\pm1.3x10^{-10}$ hormone level/total protein amount; LFs: $2.2x10^{-9}\pm2x10^{-10}$) while not significantly different E_2 levels were detected ($P\geq0.05$). *In vitro* data were matched with follicular diameter by PCA, revealing that LFs are a sub-cluster of SFs data, suggesting higher gene expression variability in SFs vs LFs. Heatmap hierarchical clustering revealed inverse relationship between *AMHR2* and *CYP19A1* expression levels. *CYP19A1*, *FSHR* and *CCND2* were downregulated in LFs while upregulated in SFs, oppositely to what observed for *LHCGR* and *GPER*. *XIAP* and *TP53* have similar expression levels in SFs and LFs. The present study confirms different expression of follicle maturation genetic markers.

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P187

In vitro effect of visfatin on progesterone and prostaglandins' secretion by the porcine corpus luteum. Involvement of insulin receptor and different kinases' signalling pathways

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Visfatin is one of adipokines that particularly regulates metabolic homeostasis. Literature data of the last decade indicate also that visfatin participates in the regulation of ovarian follicles' steroid synthesis and oocyte maturation in women, mice, hens, and cows. However, there is still a gap in knowledge about the effect of this adipokine on the corpus luteum (CL) functions. Our previous study documented visfatin mRNA and protein expression in the porcine CL. Therefore, the aim of the present study was to determine the impact of visfatin on endocrine functions of the porcine CL during the estrous cycle. Corpora lutea were collected from gilts on days 2–3, 10–12, 14–16 of the estrous cycle and luteal cells were treated with visfatin (1, 10, 100 ng/ml) alone or together with visfatin blocker FK866 (10 μM). Then, we analyzed the secretion of progesterone (P_4), prostaglandin E_2 (PGE_2) and $F_{2\alpha}$ ($PGF_{2\alpha}$) as well as protein expression of steroidogenic enzymes (StAR, CYP11A1, 3βHSD) and prostaglandins' receptors (PTGER1, PTGFR). Moreover, we investigated the impact of visfatin (10 ng/ml) on activation of MAPK, AMPK, and AKT kinases as well as the involvement of these kinases and insulin receptor (INSR) in visfatin action. Statistical analysis was performed using one-way ANOVA and Tukey's post-hoc test. The results of the study demonstrated that visfatin decreased P_4secretion by luteal cells from days 2-3 and 14-16, while increased on days 10-12 of the cycle. These results were confirmed by visfatin stimulatory effect on protein levels of StAR, CYP11A1 and 3βHSD on days 10-12. We noted that visfatin enhanced PGE_2 secretion by the cells from days 2-3 and 10-12, while decreased PGF_{2a} release on days 14-16 of the cycle. These changes were also accompanied by increased luteal PTGER1 protein expression on days 10-12 and decreased PTGFR on days 14-16 of the cycle. Treatment with the visfatin blocker, FK866, suppressed the observed visfatin effect on steroids' and prostaglandins' secretion. Interestingly, visfatin in time-dependent manner stimulated MAPK, AKT and AMPK pathways. Moreover, MAPK, AKT, AMPK and INSR were involved in visfatin effect on P_4, while MAPK and INSR on prostaglandins' secretion. The obtained results indicate that visfatin affects luteal endocrine functions, depending on the phase of the estrous cycle, and could be the new regulator of the porcine ovary.

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P188

Prognostic Value of Hormonal Examination in Adolescent Girls with Polycystic Ovarian Syndrome

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Relevance
PCOS is a multifactorial heterogeneous disease associated with endocrine, reproductive, and metabolic manifestations. The relevance of the PCOS problem is determined by its high prevalence worldwide among women of childbearing age (5 - 20%). It is worth noting that the main reproductive signs of PCOS appear in late prepubertal and pubertal periods.
The aim is to carry out a comparative analysis of hormonal indicators in PCOS
Materials and Methods
A total of 120 adolescent girls aged 14-18 years, diagnosed with polycystic ovarian syndrome, were included in the study. Hormone balance was determined using a «PW 300 M Chemistry Analizator» (USA). The results obtained were statistically processed by determining the mean mathematical limit (m), standard deviation, mean error of mathematical limit (m). The results were considered statistically significant at $P<0.05$. Statistical studies were performed using Microsoft Excel and Statistica 10.0 software.
Results of discussion
The most typical manifestations of PCOS that appeared from the age of menarche were: menstrual cycle (86%), mostly by the type of oligomenorrhea (52%); hirsutism (81.2%). Hormonal analysis revealed a wide variability in FSH in adolescent girls from 3.4 to 64.3 IU/l, and from 2.8 to 7.2 IU/l in the control group, which is associated primarily with insufficient hormonal function of the ovaries. The analysis of the LH content revealed rather high LH values in the blood serum of adolescent girls ($13.3+1.6$ IU/l). The LH/FSH ratio was $2.3+0.4$ (normal-. Thus, changes in the gonadotropin indices are already a precursor of functional disorders of the hypothalamic-pituitary system of menstrual function regulation. In patients with polycystic ovary syndrome individual values of testosterone ranged from 1.8-3.9 (mean $3.1+1.2$ nmol/l). The serum AMH content in LPS patients ranged from 2.4 ng/ml to 18.0 ng/ml and averaged 7.6 ± 0.8 ng/ml, which was significantly ($P<0.001$) higher than its content in healthy women (2.5 ± 1.3 ng/ml). The volume of each ovary ranged from 11.3 to 16.0 cm3 and was larger than that in women without PCOS. The mean number of antral follicles in the ovary was 8.8 ± 1.0 (11 to 12), which was also greater than in women without PCOS.
Conclusions
In PCOS, there is an imbalance between the amount of androgens, antimullerian hormone (AMH), LH and FSH, which results in the failure to select the 'dominant' follicle despite relatively rapid and early follicle growth.

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P189

45X/46XY Mosaicism in a Male as a Rare Cause of Absence of Sexual Interest

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Introduction
The incidence rate of 45X / 46XY karyotype and variants has been reported as 1 / 15,000 live births and is rare. The phenotypic spectrum of patients with 45X / 46XY varies widely from women with Turner syndrome to normal androgenized men. In adult male infertility studies, 45X / 46XY karyotype cases diagnosed as a result of genetic screening have been reported. However, there are case reports showing that, despite their normal appearance, these patients may have dysgenetic testes that can result in decreased testicular function, delayed puberty, and infertility. In this article, we will describe a rare, apparently normal 45X / 46 XY male case.
Case Presentation
A 33-year-old male patient consulted the endocrinology department for primary infertility. He suffered from erectile dysfunction. He had been married for one year but had never had an intercourse with his partner. He reported a normal pubarche at the age of 14 with normal development of facial hair however, in time, had lost interest for the opposite sex and had no sexual partner at all. Physical examination was unremarkable and axillary and pubic hair development were consistent with Tanner Stage V. Stretched penile length was 11 cm. Scrotal ultrasonography showed bilateral small testes: (right testicular volume:12x17x28mm and the left testicular volume: 115x23x25mm) Bilateral epididymis were normal in size and sonographically homogenous. Penile ultrasonography suggested findings of venous insufficiency. Laboratory analysis revealed hypergonadotropic hypogonadism. Complete blood count, liver and kidney function tests, and thyroid function tests were normal in the examinations. FSH was 33.1 mIU / mL, LH was 17.44 mIU / mL and T. testosterone 277.4. Azoospermia was detected in semen analysis. Karyotype analysis showed, 46XY (13) 45, X (17) mosaicism.
Conclusion
45, X / 46, XY mosaicism can occur with a wide variety of phenotypes and patients without gender growth retardation can be easily ignored. It can affect hormonal balance, gonadal development, growth, and fertility. Chromosomal abnormalities should be considered in patients with absence of sexual desire and erectile dysfunction and hypergonadotropic hypogonadism, including phenotypically normal males.

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P190

Mitochondrial uncoupling proteins (UCPs) regulate mitochondrial function in mouse Leydig Cells: a possible role on steroidogenesis?

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Introduction
Mitochondrial uncoupling proteins (UCPs) are transmembrane channels present in the inner mitochondrial membrane whose function is the transport of protons and small substrates between the intermembrane space and the mitochondrial matrix. UCPs are key regulators of cellular metabolism, including mitochondrial function, oxidative phosphorylation, and reactive oxygen species (ROS) production. UCPs' dysfunction has been associated with the onset of metabolic diseases, such as obesity and diabetes mellitus. In men, metabolic diseases are closely linked to hypogonadism and lower testosterone production in Leydig cells, however, the molecular mechanisms are still poorly understood. The dysfunction of UCPs could play a role in the crosstalk between metabolic diseases and hypogonadism but their expression and function in Leydig cells is still unknown.
Aim of the study
The aim of this study was to identify the expression of UCP1, UCP2, and UCP3 in mouse Leydig Cells (mLCs). Additionally, the influence of UCPs on the mitochondrial function was assessed, through its inhibition by genipin, a selective UCP inhibitor.
Materials and methods
Culture of mouse Leydig cells (BLTK1 cell line) were established ($n = 10$). Total RNA was extracted and *Ucp1*, *Ucp2*, and *Ucp3* mRNA expression were assessed by RT-PCR. UCP1-3 protein expression was determined by Western Blot and immunofluorescence. To assess UCPs function, mLCs were treated with genipin (0.5, 5, 50 and 100 μM). After 24 h treatment, cellular proliferation and viability were evaluated. Mitochondrial function was accessed by Seahorse XF Cell Mito Stress assay kit.
Results
We were able to identify both the mRNA and protein expression of UCP1-3 in mLCs. The inhibition of UCPs decreased cellular proliferation and viability of mLCs. Additionally, the mitochondrial function was severely affected by UCPs' inhibition.
Conclusion
In this work, we were able to identify for the first time, to the best of our knowledge, the expression of UCP1-3 in mLCs. Our data highlight that UCPs are modulators of mLCs mitochondrial function, suggesting a potential regulatory role of UCPs on steroidogenesis. Taken together, the discovery of UCPs in Leydig cells opens the path for future studies focusing on the molecular mechanisms responsible for the metabolic diseases-induced male hypogonadism.

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P191

Effects of gender affirming treatments on sex hormone levels, mental well being and body image quality of life in transgender individuals

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Table 1 (Abstract P191)

	Transfemale			Transmale		
	GnRH Analog + CSH Treatment (n:5)	CSH Treatment (n:13)	*p*	GnRH Analog + CSH Treatment (n:7)	CSH Treatment (n:12)	*p*
Age (year)	21,6±3,5	26,6±6,0	0,1	19,1±1,46	27,2±4,73	**0,001**
BKI (kg/m2)	22,2±3,8	25,1±6,2	0,6	25,0±4,7	25,1±7,01	0,65
Smoking						
Present	n:1	n:7	0,3	n:5	n:9	0,8
Absent	n:4	n:6		n:2	n:3	
Gender Affirming Surgery (GAS)						
Surgery (GAS)	n:4	n:7	0,3	n:2	n:9	0,04
Present	n:1	n:6		n:5	n:3	
Absent						
Supression of erections/-menstruation	3,7±2,06	2,2±1,5	0,3	1,0±0,0	5,2±3,7	**0,001**
Onset of Treatment Benefit (month)	4,1±1,9	3,67±1,7	0,4	7,8±8,3	9,5±8,5	0,31
Initial Testosterone (ng/ml)	6,3±2,1	5,4±2,9	0,83	0,4±0,18	0,6±0,32	0,24
Initial Estradiol (pg/ml)	28,9±10,2	44,8±28,4	0,4	99±40,7	88,4±59,2	0,50
Testosterone change in 6th/12th month (ng/ml)	-5,8±2,1 -5,9±2,2	-2,3±2,1 -3,4±-1,6	**0,01** **0,02**	1,77±0,51 2,3±0,89	3,49±1,93 6,2±2,36	**0,018** **0,010**
Estradiol change 6th/12th month (pg/ml)	22,0±39,1 46,1±29,1	26,6±45,3 20,7±33,8	0,9 0,1	-30,2±19,2 -15,2±12,9	-63,3±40,5 -70,1±59,7	**0,034** **0,027**
PHQ-9 score	2±1,4	6,5±10,0	0,64	9,8±8,3	4,4±4,1	0,14
BIQLI score	45±1,4	30,0+25,9	0,85	16,3±31,3	43±7,4	**0,033**

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Objective
Transgender individuals endure gender dysphoria and incongruence between physical appearance and gender identity. We aimed to investigate effects of gender affirming treatments on sex hormone levels, mental well being and body image quality of life in these individuals.
Material and Method
This is a descriptive cross sectional study. Transgender individuals who were transitioned from pediatric to adult care (n: 12) and who were formerly followed up in endocrinology department for at least six months (n:25) were included. Groups consisted of female to male (FTM, n: 19) and male to female (MTF, n:18) transgender individuals. Treatments were classified as gender-affirming hormone therapy [GAHT: GnRH analog (GnRHa) and/or cross sex hormone treatment (CHT)] and gender affirming surgery (GAS). Participants were invited to complete Patient Health Questionnaire (PHQ-9) and Body Image Quality of Life Inventory (BIQLI). Sex hormone levels, onset of virilization or feminization symptoms, patient outcome questionnaire scores were compared.
Results
Demographic and clinical characteristics are demostrated in Table-1. PHQ-9 scores were correlated with age ($P=0,03$, r:-0,56), BIQLI score ($P=0,006$, r:-0,674), onset of treatment benefit ($P=0,03$, r: 0,58) and BIQLI scores were correlated with age ($P=0,02$, r:0,57) and presence of GAS ($P=0,006$, r:0,67) among transmale individuals. In Transfemale individuals BIQLI scores were correlated with age ($P=0,008$, r:0,601), PHQ scores ($P=0,002$, r:-0,936), testosterone levels on 6th and 12th months ($P=0,02$, r:-0,93 and $P=0,02$, r:-0,93, respectively).
Conclusion
Apart from GAHT, age and presence of GAS are prominent factors effecting body image quality of life and PHQ-9 scores in transgender individuals.
Keywords: gender dysphoria, gender affirmation treatment, body image quality of life

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P192

Progesterone Limits the Increase in p53 caused by Dexamethasone Treatment in the Labyrinth Zone of Rat Placenta

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Introduction and objectives
Placental apoptosis plays important roles in both normal physiological and abnormal pathological placental development. Fetal growth is highly dependent on the placenta, thus any disruption in placental formation may lead to intrauterine growth restriction (IUGR). The rat placenta consists of a basal zone (BZ) and labyrinth zone (LZ). The BZ is the major site of placental hormone production and it goes under physiological apoptosis at the end of term. While the LZ is the major site for nutrient/waste exchange which is essential till the end of term. Dexamethasone (DEX) is a synthetic glucocorticoid that stimulates placental apoptosis and inhibits feto-placental growth which leads to IUGR. Research on rats indicated that DEX-induced IUGR is associated with placental apoptosis. In the LZ of IUGR placentas the activity of p53 a tumor suppressor protein that initiate apoptosis is increased. Progesterone (P), on the other hand, has been shown to inhibit placental apoptosis. Furthermore, research conducted on human and rat placentas showed that low maternal progesterone level during pregnancy is associated with low fetal and placental weights and development of IUGR. We hypothesize that P will reverse the apoptotic effects of DEX-induced IUGR
Methods
Pregnant Sprague-Dawley rats received daily intra-peritoneal injections of either saline (C group), DEX (0.2 mg/kg; DEX group), P (5 mg/Kg/day: P group) or mixture of DEX + P (0.2 mg/kg + 5 mg/Kg/day: DEX+P group) starting from 15 days of gestation (dg) to 21 dg. Gene and protein expressions of p53 in the BZ and LZ were investigated by RT-PCR and Western blotting in all groups.
Results
In BZ, DEX decreases the p53 mRNA and protein expression while P treatment increases it and returned it normal levels ($P<0.05$). p53 mRNA expression decreased also in DEX group compared to that in P ($P<0.05$). In P group, p53 protein expression was lower compared than in C and DEX+P ($P<0.05$). In the LZ, DEX increases the p53 mRNA and protein expression while P treatment decreases it but not to normal levels ($P<0.05$). p53 mRNA and protein expression was higher in P group compared to C ($P<0.05$). Also in P group p53 mRNA expression was higher than that in DEX+P, while the p53 protein expression was lower than that in DEX group ($P<0.05$).
Conclusions
In the LZ, P reduces the high level of p53 caused by DEX which could be associated with reduction in apoptosis.
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P193

Occurrence of vertebral fractures, hypovitaminosis D, and osteoporosis among postmenopausal women living in rural areas

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Background
The likelihood of developing a fragility fracture rises with age. Osteoarthritis, osteoporosis, and hypovitaminosis D are all extremely common diseases, with 50% of women and 20% of men experiencing a fragility fracture at some point in their lives.
Objectives
First, compare the occurrence of osteoporosis, fragility fractures, and risk factors such as low vitamin D levels, low bone mineral density, and the presence of other illnesses that predispose to their occurrence in two groups of postmenopausal women living in different populations centers (rural vs. urban); second, observe the impact of low socioeconomic status, or poverty.
Material and Methods
Study participants included 260 postmenopausal women, 115 (31.6%) of who resided in rural areas and 145 (68.2%) in urban areas. In addition to other biochemical measurements, 25-hydroxyvitamin D and parathyroid hormone were identified among the information on risk factors for osteoporosis. Along with lateral X-rays of the dorsal and lumbar spine, bone densitometry was done on the proximal femur and the lumbar spine. The statistical analysis was performed utilizing SPSS® (Statistical Package for the Social Sciences) version 18.0 of the statistical program. The means were compared using the Student's t test or the Wilcoxon test, and the percentages were compared using the Chi-squared test (in the case of non-normality).
Results
Compared to women who resided in urban areas, rural women were older, shorter, heavier, and had a higher body mass index. There was a higher frequency of poverty, as well as higher levels of obesity, arterial hypertension, diabetes mellitus, and densitometric osteoporosis, among women from rural areas. The rural women exhibited greater rates of vertebral fractures and hypovitaminosis D, as well as poorer values for bone mineral density in the lumbar spine. Poverty, obesity, vertebral fractures, BMD in the lumbar spine, and levels of 25-hydroxyvitamin D were the factors that were independently linked to residing in rural areas.
Conclusions
According to this study, postmenopausal women who reside in rural areas are more likely to be poor, have lower vitamin D levels, have lower lumbar spine BMD, and have a greater incidence of osteoporosis and vertebral fractures. These women's increased rates of obesity, arterial hypertension, and diabetes mellitus may all be contributing causes to their socioeconomic status as poor.
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P194

Masculinizing Hormone Therapy: What Happens to Estradiol and To Total, Free and Biovailable Testosterone?

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Introduction
Masculinizing Gender-Affirming Hormone Therapy (GAHT) generally aims to induce testosterone levels equivalent to those of cisgender men and to reduce estradiol levels. There are no studies about bioavailable testosterone in this population.
Aims
To determine the variation of the serum levels of sexual hormones in transmasculine people under GAHT and study the correlations between them and with BMI.

Table 1 (Abstract P194)

Months	M0	M6	M12	M24	M36	M60
N	78	15	6	13	11	12
Total testosterone (ng/ml)	0.34 (0.23-0.49)	4.26 (2.65-6.90)	4.78 (1.59-12.47)	4.53 (4.07-6.33)	4.93 (4.22-6.12)	4.20 (2.99-6.29)
Free testosterone (pg/ml)	1.66 (1.04-2.42)	12.22 (7.91-15.33)	10.55 (4.76-17.17)	10.71 (7.76-14.27)	9.84 (8.54-13.12)	7.95 (6.58-11.46)
Bioavailable testosterone (ng/ml)	0.10 (0.07-0.17)	2.84 (1.77-4.43)	2.51 (1.10-2.98)	2.80 (2.21-4.76)	2.76 (2.28-3.51)	2.65 (1.85-5.02)
Estradiol (pg/ml)	62.45 (34.08-132.00)	38.85 (29.08-60.08)	30.10 (25.48-43.08)	41.40 (29.00-65.80)	34.90 (24.90-74.00)	22.70 (18.50-55.25)

Methods
Longitudinal retrospective study which included adult transmasculine patients currently under follow up at our center. Data collected at 0, 6, 12, 24, 36 and 60 months of GAHT were analyzed.
Results
A total of 91 patients were included (85 trans men and 5 non-binary people). At the first visit at our center their median age was 24(20-28) years and their median BMI was 24.1(21.5-29.1) Kg/m^2. The median serum concentration of sexual hormones during follow-up was: Comparing with M0, at every visit there was a significant increase ($P<0.001$) in the serum level of testosterone – total, free and bioavailable. The reduction in the estradiol serum level only reached statistical significance at M60 ($P=0.005$). However, if the patients that underwent oophorectomy are excluded from the analysis, this reduction also becomes not significant at M60 ($P=0.125$). No correlation was found between the serum levels of estradiol or testosterones and BMI. Total testosterone serum levels showed a strong positive correlation with those of free and bioavailable testosterone (0.854 and 0.954, $P<0.001$). Only total testosterone serum levels reached statistical significance when testing the correlation with estradiol serum levels (-0.215, $P=0.010$).
Conclusions
Masculinizing GAHT alone does not seem to be enough to significantly reduce estradiol serum levels, but oophorectomy seems to make a difference. Total testosterone correlates properly with free and bioavailable testosterone, which may imply that measuring the latter may be futile in most situations. Similarly to other studies, no correlations with BMI were found.

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P195

School Failure in Type 1 Diabetic in Transition Period

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Introduction
Adolescence represents the passage from childhood to adulthood, this transition is characterized by physical and psychological transformations as well as many social challenges. The presence of chronic disease such as diabetes makes this a major challenge.
Purpose
Describe the impact of diabetes on the school career of adolescents during the transition period.
Methods
Descriptive study involving 79 young people aged 15 to 20 years cared for in hospitalization or in transition diabetology consultation.
Results
The average age is 16.2 years, divided into 38% young men and 62% young girls. The duration of diabetes evolution is 7.93 $\pm$ 4.02 years. Late pediatric transition was noted in 5% of patients. Glycemic control is poor (average HBA1c = 11.19 $\pm$ 2.12%). Diabetic retinopathy is present in 7.5%. We note that 29% have left school voluntarily, 59% say they have academic difficulties, only 12% say they are fulfilled and plan to go to higher education. The main causes reported are; the stigmatization of the entourage and denigration of the person in 35%, 28% are ashamed to inject themselves in a public environment, 12% incriminate the number of hospitalizations, 29% mark the frequency of hypoglycaemia at school, and alone 7% blame the decline in visual acuity.
Conclusion
Adolescent diabetes is a major challenge for the attending physician, the patient and his family, requiring close monitoring, psychological care and education of those around him

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P196

Metabolic syndrome in Turner syndrome

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Introduction
Turner syndrome (TS) is a feminine chromosomic disease, defined as the partial or total loss of the X chromosome. Classic phenotype includes growth and pubertal retardation as well as a characteristic dysmorphic syndrome. Other accompanying comorbidities are frequently associated with TS such as metabolic diseases: overweight, diabetes, hypertension (HTA) and dyslipidemia. Through this report we aim to determine the frequency of metabolic diseases associated with TS and to identify the karyotypes mostly associated with these conditions.
Methods
We carried out research that took place in the Endocrinology department of Hedi Chaker Hospital, between 1990 and 2021. We enrolled in our study patients with TS. Overweight is defined by a BMI between 25 and 29,9 kg per m^2, while obesity corresponds to a BMI above 30 kg per m^2.
Results
Our cohort enclosed 45 patients. The mean age of diagnosis was 16 years. The vast majority were diagnosed between 10 and 20 years (44.2%). Three were diagnosed after 40 years. A wide range of chromosomic abnormalities were noted in our series, dominated by 45, X karyotype (49%). The other karyotype findings were: mosaicism without structural abnormalities of X chromosome (31%) and mosaicism with structural variants of X (20%). Most of our study population had a normal BMI (55.6%). Only one patient was obese (2.2%) whereas eight had overweight (17.8%). The frequency of diabetes and prediabetes was 9.7% and 25.8%, respectively. At a mean age of 24.8 $\pm$ 10.5 years, nine patients were diagnosed with hyperlipidemia (29%): type IIa in three cases and type IV in five cases while a mixed hyperlipidemia was found in one case. As for hypertension, it was found in 13.3 % of our study population. Concerning the genotype-phenotype correlation, we noted a higher BMI in patients with structural abnormalities of X: 21.02 kg/m^2 vs 20. 37 kg/m^2 and 20.24 kg/m^2 in 45, X and mosaicism without structural abnormalities, respectively ($P=0{,}908$). However, these differences were non-significant. Otherwise, there was no specific karyotype associated with metabolic conditions ($P=0{,}660$).
Conclusion
Metabolic disorders are frequent in TS and thus an annual screening of these diseases is mandatory. Patients with structural abnormalities seem to be more prone to develop overweight. However, larger studies are needed to confirm these findings.

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P197

Polycystic ovary syndrome phenotype and therapeutic outcomes

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Introduction
Polycystic ovary syndrome (PCOS) is a common endocrinopathy affecting women of reproductive age. PCOS has two phenotypes, obese and lean, the latter being a much less common presentation of the syndrome.
Aim
Compare PCOS outcomes in patients with obese PCOS and patients with lean PCOS.
Methods
A retrospective, single-center, descriptive and comparative study including patients with PCOS followed at the endocrinology department of Hedi Chaker University Hospital of Sfax, Tunisia. G1 included patients with obese PCOS and G2 included patients with lean PCOS.

Results
We included 50 female patients, of which 28 had obese PCOS. G1 patients had significantly higher BMI, waist circumference, weight and systolic blood pressure. Menstrual cycles disturbances was equally reported in the two groups while hirsutism was more common in G1 (96,7% vs 72.1%; $P=0.019$). Fertility issues were more frequent in obese PCOS patients (71.1% vs 45.2%; $P=0.036$). Response to therapeutic measures was more favorable among G2 patients as they had a more significant reduction in Ferryman and Gallway score ($P=0.01$). However, weight loss and normalization of menstrual cycles were comparable between the two groups ($P=0.7$ and $P=0.22$ respectively).
Discussion & Conclusion
PCOS phenotype seems to dictate some aspects of the therapeutic outcomes. Insulin resistance, low grade inflammation, adherence to treatment and psychosocial factors may be some of the main underlying explanations. Mackens *et al*. demonstrated that cumulative birth rates were lower after ovarian stimulation in obese PCOS patients. In a recent prospective study; Sachdeva *et al*. reported higher resistance to Clomiphene among obese PCOS patients. A phenotype-based, personalized approach needs be adopted in PCOS management.
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P198

The Effect of Menopausal Status On Anthropometric Measurements and Nutritional Status
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Menopause defines the period in which women's menstrual periods cease permanently, significant hormonal changes begin, and fertility is lost. In addition to the fact that menopause causes body weight gain, it has been found that body weight gain can negatively affect the menopausal process. In this study, the relationship between food consumption and body composition changes that may be caused by the menopause period and menopausal symptoms was investigated. In the study, 66 menopausal women without any chronic disease were evaluated through sociodemographicform, anthropometric measurements, menopausal symptoms evaluation scale (MRS), and 3-day food consumption record. Participants were evaluated as two groups, MRS <15 (n:16) and MRS>15 (n:50). The mean age of the participants evaluated in the study was 51.7 ± 4.6 years. It was found that the mean menopause age was 48 ± 3, the mean time spent at menopause was 3 ± 2 years, and the mean body weight gain during the menopause period was 6 ± 4 kg. The mean MRS total score was 22 ± 10, the somatic complaints factor mean score was 8 ± 4, the psychological complaints factor mean was 8 ± 5, and the urogenital complaints factor mean was 5 ± 3. It was found that the averages of body mass index (kg/m2), waist circumference (cm), hip circumference (cm), and neck circumference (cm) of the women with MRS>15 were significantly higher than the averages of the woman with MRS <15 ($P<0.05$). Dietary intake of total fat, saturated fatty acids, unsaturated fatty acids, and eicosapentaenoic acid were positively correlated with somatic complaints in menopausal women ($P<0.01$), the amount of protein consumption ($P<0.01$), and animal protein ratio ($P<0.05$) in menopausal women was significantly and negatively correlated with somatic symptoms, and the amount of energy intake (both total intake and kcal intake per body weight) was positively correlated with somatic complaints ($P<0.01$). As a result of the research, it was thought that somatic and psychological complaints would decrease with a healthy and balanced diet in menopausal women.
Keywords
Menopause, Nutrition, Body Mass Index, Menopausal Symptoms Evaluation Scale
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P199

Estetrol: estrogenic activity and coregulator profiling
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Estetrol (E4) is a natural estrogen produced by the human fetal liver during pregnancy. E4 is the estrogenic component of a new combined oral contraceptive and is also in development for its use as menopausal hormone therapy. E4 displays a selective binding to human estrogen receptors (ER). In humans, after oral administration, E4 undergoes phase 2 metabolism leading to the formation of the two major metabolites E4-3-glucuronide and E4-16-glucuronide. The objectives of this study were (*a*) to compare the estrogenic activity of E4 to estradiol (E2) and ethinylestradiol (EE) induced via both ERα and ERβ; (*b*) to determine the estrogenic activity of E4 metabolites and (*c*) to characterize the ER coregulator recruitment profile induced by E4. In order to determine the estrogenic activity of E4 and its metabolites, a luciferase reporter assay (ER-CALUX bioassay) was conducted. Briefly, human osteoblastic U2-OS cells stably expressing ERα or ERβ, as well as an estrogen-responsive luciferase reporter gene, were exposed to increasing concentrations of E4 or metabolites for 24 h. Reference estrogens E2 and EE were also included as comparators. The coregulator recruitment assay was performed with the MARCoNI technology, and the binding pattern of ERα to 154 coregulator-derived peptides was analyzed. E4 displayed estrogenic activity in both ERα and ERβ assays. However, the potency of E4 was lower than that of E2 or EE. In addition, the potency of the metabolites was several hundred-fold lower than the potency of the parent molecule E4. The EC_{50} value and relative transactivating potency of E4 and the metabolites with E2 and E4 as a benchmark, respectively, are presented below:
In conclusion, E4 induces transcriptional activity via both ERα and ERβ, although with a lower potency than E2 and EE. E4 induces the recruitment of the same profile of coregulators to ER as E2, suggesting that E4 and E2 induce transactivation via the same molecular mechanisms. Glucuronidation of E4 leads to the formation of metabolites with negligible estrogenic activity.

	EC_{50} (M) [Relative potency]	
	ERα	ERβ
E4	6.2×10^{-10} [0.0037]	1.2×10^{-8} [0.0044]
E2	2.3×10^{-12} [1]	5.3×10^{-11} [1]
EE	8.7×10^{-13} [2.6]	2.5×10^{-10} [0.21]

	EC_{50} (M) [Relative potency]	
	ERα	ERβ
E4-16-Gluc	1.7×10^{-6} [0.0017]	9.0×10^{-6} [0.0024]
E4-3-Gluc	1.1×10^{-5} [0.00026]	*
E4	2.9×10^{-9} [1]	2.2×10^{-8} [1]

*No full curve obtained
Overall, E4 and E2 induced a similar coregulator recruitment profile.

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P200

Effect of Overweight On the Course of Early Menopause in Women
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Purpose
To study the role of varying degrees of overweight in the course of menopause.
Materials and methods of the study
The study involved 278 women in the menopausal period aged 40 to 46 years, of which the main group (MG) consisted of 218 women with overweight and obesity of varying degrees. The control group (CG) included 60 women with normal body weight and a waist
Results of the study
As a result of the studies, we found that overweight (BMI - 25.0-29.9 kg/m2) was observed in 62 women (28.4%) out of 218 examined in the main group; in other cases, obesity of various severity (BMI - 30.0-41.2 kg/m2). 72.0% of overweight women noted an increase in BMI after 36 years, i.e. at the beginning of the late reproductive period, while women with obesity of varying severity after 40 years. In the CG, 33% of women from the CG noted weight gain after 36 years, although these indicators did not go beyond the normal range. Circumference of 80 cm. Women with overweight and obesity had a high comorbidity, so 36% of women from the MG had arterial hypertension, 22% had coronary heart disease, 10% had chronic venous insufficiency, and 10% of women noted arrhythmias. I would especially like to highlight the frequency of gastrointestinal diseases in women with OH, of which 42% is cholelithiasis, 62.4% is chronic gastritis, 18.3% is chronic colitis, 6% is peptic ulcer and 28.4% is chronic pancreatitis. The frequency of occurrence of gynecological pathology also depended on BMI, so in women with overweight in 58.4% of cases, uterine fibroids, adenomyosis, etc. were noted, while in the CG this percentage was 13.8%. The range of clinical symptoms in women with overweight, obesity and normal body weight differs, the former and the latter are dominated by headaches (in 95.0%), irritability (in 72.5%), sleep disturbance (in 67.5%), muscle and joint pain (in 62.5%), sexual dysfunction (in 52.5%). The climacteric syndrome in obese patients is more

severe and often manifests with climacteric symptoms such as palpitations and tachycardia, excitability, dizziness, muscle and joint pain, hot flashes, and sexual dysfunction.
Conclusion
Thus, menopause is associated with an increased prevalence of overweight. Increased central fat deposition, reduced peripheral fat deposition, and ectopic fat accumulation contribute to cardiometabolic abnormalities, resulting in an increased prevalence of metabolic syndrome after menopause.

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P201

Dopamine Agonist-Resistant Prolactinoma: Case report and literature review

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The therapy of hyperprolactinemia with dopamine agonists (DAs) is highly effective in the majority of cases (1). However, some patients fail to achieve normal prolactin levels and develop drug resistance towards prescribed medicine. This case study describes a medical history of The Georgian National Institute of Endocrinology patient, with a drug-resistant hyperprolactinemia and inability to conceive. The patient's MRI scan result has not indicated incidence of prolactinoma.
The Case Study
A 27-year-old female visited ambulatory clinic with severe headache and amenorrhea. The patient asked to reassess previously prescribed treatment protocol. According to her medical history, she has been diagnosed with hyperprolactinemia and nodular goiter, since she was 14 years old. The patient has been prescribed the dopamine agonist cabergoline (CAB, 0.25 mg, to be taken twice a week). The prolactin levels remain high despite dose escalation. A pituitary MRI with contrast was performed twice: at aged 20 and aged 26. Both scans have not indicated any abnormal lesions. The patient has denied taking any other medicine or recreational drugs.
First ambulatory visit
Prescribed medicine CAB 1.75 mg twice a week (3,5 mg per week). Levothyroxine 25 mg daily. Blood test Showed increased prolactin level - 56,94 ng/ml. (normal range: nonpregnant females: 2 to 29 ng/ml) (2) The blood test was conducted to check hyperprolactinemia level due to non-reactive isoforms. The fraction of polyethylene glycol (PEG)-precipitated (complexed) prolactin was <40 % of total prolactin, therefore the specimen was considered negative for macroprolactin. The further evaluations of pituitary hormones didn't reveal deviation from the norm. Bromocriptine (2,5 mg) 1/2 pill was added to the patient's existing prescription.
Second ambulatory visit (after six months)
The prolactin level has increased up to 61,10. ng/ml. Updated prescription: Quinagolide 150 mg daily. CAB and Bromocriptine were discontinued due to low efficacy.
Third ambulatory visit
(after three months): regular menses has been restored. On the third regular menstrual cycle, a successful ovulation has been confirmed by appearance and disappearance of a dominant follicle on transvaginal ultrasound (TVUS), performed every third day and by blood test: mid-luteal phase progesterone -12 ng/ml.(3) The prolactin decreased by - 30 ng/ml (1.8–20).
Conclusion
We concluded that partial resistance can be managed by drug shifts, leading to hormonal control of initially resistant patients. As a result the restoration of a normal gonadal axis can be achieved.

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P202

The effect of thyroid function and estrogen levels on Body Mass Index in women of reproductive age

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Background
Obesity in women of reproductive age has a number of negative metabolic consequences, including dyslipidemia, type 2 diabetes, cardiovascular diseases, certain types of cancer. It is associated with increased ovulatory dysfunction, complications during pregnancy, endometriosis and endocrine abnormalities, including thyroid dysfunction.
Aim
To study the prevalence of BMI and its correlation with thyroid disorders, female sex hormones and presence of endometrial hyperplasia.
Materials and methods
A single-center, retrospective, observational study included 250 women aged between 18-45 years. The anthropometric measurements, laboratory and outcomes data were compared.
Results
Additional statistical analysis included correlation matrix between several numeric variables (Table 1). Investigation the presence of association between seven numeric variables revealed six statistically significant correlations. Specifically, values of BMI negatively correlated with estradiol ($r=$-0.14) and T4 levels ($r=$-0.18). Also, a statistically significant positive correlation was detected between BMI and TSH variables ($r=0.21$). The strongest correlation was observed between LH and FSH levels ($r=0.77$). Elevation in values of LH corresponds to an increase in FSH levels. Estradiol levels possessed a low positive correlation with LH levels ($r=0.16$). The TSH is negatively related to T4 variable ($r=$-0.17). Lastly, the association between T4 and T3 levels entailed a moderate positive correlation ($r=0.6$). Moreover, 132 (84.08%) women with BMI >30 and 86 (95.56%) women with BMI <30.
Conclusion
Obesity in women is one of the prevalent global public health problem that crucial in all stages of women's life. Weight gain in women of reproductive age leads to a low estradiol level and, as a result, to ovulatory dysfunction, thus underweight women have an increased risk of experiencing early menopause. We suggest that the relationship between obesity, low estradiol, thyroid disorders are bidirectional. All values are three common conditions and there is an intriguing relationship between these entities, of course, further investigation is warranted in this field.

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P203

Predictive factors of infertility among patients with polycystic ovary syndrome

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Introduction
Polycystic ovary syndrome (PCOS) is occurring in approximately one in seven women. Infertility is a major issue in PCOS. Recognizing patients with higher risk of infertility is still a matter of debate.

Table 1 Correlation of BMI level with clinical/biochemical variables.

	BMI	Estradiol	LH	FSH	TSH	T4	T3
BMI	1.0000						
Estradiol	-0.1383*	1.0000					
LH	0.0047	0.1640*	1.0000				
FSH	0.0331	-0.1180	0.7730*	1.0000			
TSH	0.2053*	0.0365	-0.0725	-0.0545	1.0000		
T4	-0.1847*	-0.0024	-0.0461	-0.0626	-0.1716*	1.0000	
T3	0.0454	-0.0421	-0.0155	-0.0129	-0.0742	0.5987*	1.0000

BMI, body mass index; LH, luteinizing hormone; FSF, follicle-stimulating hormone; TSH, thyroid stimulating hormone; T4, free thyroxine
*$P<0.05$

Aim
Study the predictive factors of female infertility in patients with PCOS
Methods
A retrospective, single-center, comparative and analytical study including patients with PCOS followed at the endocrinology department of Hedi Chaker University Hospital of Sfax, Tunisia. G1 included PCOS patients with inability to conceive and G2 included fertile PCOS patients.
Results
We compared two groups. Of whom 30 had fertility issues (G1). And 20 fertile patients. Age was comparable between the two groups. Using univariate analysis, G1 patients had higher frequency of menstrual disturbances (87.2% vs 63.6% $P=0.04$) and obesity rates (66% vs 40.7%; $P=0.035$). Other comorbidities, PCOS features, metabolic and hormonal parameters did not significantly differ between the two groups. Using multivariate analysis, PCOS phenotypes ($P=0.04$; OR = 1.2 ;CI [1.01-1.4]), menstrual disturbances ($P=0.01$, OR = 2.1, CI[1.2-2.4]) and BMI ($P=0.045$; OR = 1.12; CI[1.1-1.4]) were significantly associated with poor fertility outcomes.
Discussion & Conclusion
PCOS is one of the most common infertility causes due to its strong association with hyperandrogenism and dysovulation. In a large, multicenter study Rausch *et al*. found that BMI, hirsutism score and duration of attempting conception were the main predictors of fertility outcomes. Rafique *et al*. were able to construct an infertility risk score for patients with PCOS that featured age, BMI, oligo/anovulation, androgen excess and ovary volume on transvaginal sonography as the major conception failure determinants. In conclusion, every PCOS patient should be assessed and counseled regarding fertility derangements using a personalized approach.

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P204

Searching For The Testicles: A Medical Mystery?

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Introduction
Cryptorchidism is unilateral or bilateral absence of the testes from the scrotum. One of the differential diagnosis is congenital bilateral anorchia. Vanishing testes syndrome is associated with low serum AMH concentrations and an absent or subnormal response to stimulation with hCG. We report the case of a 22-year-old boy diagnosted with bilateral cryptorchidism and hypergonadotropic hypogonadism at the age of 17 years old. At the time of diagnosis the scrotum was empty and we could notice the failure of secondary sexual development (no pubic and axillary hair was present). The laboratory tests showed a low total testosterone = 0.11ng/ml, low free testosterone with elevated FSH = 37.30mUI/ml and LH = 14.2mUI/ml and beta-hCG. Altough congenital bilateral anorchia is quite rare, it must be distinguished from bilateral cryptorchidism. The most commonly used test is measurment of AMH, in our case: AMH < 0.010 ng/ml. The laboratory tests showed discordant values of Inhibin B: low/normal. To evaluate the testicular function, beta-hCG stimulation test was performed and the result was negative. Also, the pacient unterwent a spermiogram revealing aspermia. The patient performed multiple imaging investigations (repeated ultrasound scans, abdominal and pelvis MRI, abdominal and pelvis CT) that couldn't identify the gonads. The imaging investigations were completed with chromosomal analysys which disclosed a 46XY karyotype (Klinefelter syndrome being thus excluded). Together with the urologist, we decided to monitorize beta-hCG values and undergo an exploratory laparoscopy when the value will be five times upper high. The pacient started treatment with transdermic testosterone that was replaced after 1 year with intramuscular testosterone
Conclusions
Altough vanishing testes syndrome is extremly rare, it must be differentiated from bilateral cryptorchidism, a much more common disorder that can be complicated by testicular germ cell neoplasm if not healed in early childhood. At the same time, it must be emphasized the importance of self-examination and complete physical exam of the genital development from an early age.

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P205

HAIR-AN syndrome: about a case

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Introduction
HAIR-AN syndrome is a rare condition, which can affect up to 5% of women with hirsutism. It is formed by the initials of the following clinical entities: HyperAndrogenism (hyperandrogenism), Insulino-Resistance (insulin resistance) and Acanthosis Nigricans. It is therefore a clinical triad that is considered as a severe subtype of PCOS, characterized by insulin resistance that appears early, constant and major. We present the case of a patient with Hair-an syndrome.
Observation
This is a 19-year-old adolescent girl presenting a primary amenorrhea with a progressive hirsutism at 13 years old. This hirsutism as scored 36 in ferriman and gallwey associated with acne as well as Acanthosis nigricans, without abnormal pubertal development. Hormonal assessment showed severe hyperandrogenism with a testosterone level of 3.32 ng/ml and an SDHEA level of around 525 µg/dl (N) as well as a delta 4 androstenedione (2.41 ng/ml) and 17OHP (1.44 ng/ml) within the standards. E2 at 203 pmol/l, FSH: 4.36 ui/l, LH: 6.8 ui/l are normal. Biologically: hyperinsulinism at 97.51 µ IU/ml was objectified, as well as diabetes discovered during an OGTT. Morphologically: The pelvic ultrasound shows pubescent-looking female OGI with a large dystrophic ovary 2-10 g, without tumor process, as well as an abdomino-pelvic CT scan that returned without abnormality. Given the above features, the diagnosis of hyperandrogenism-insulin resistance-acanthosis nigricans syndrome (hairan syndrome) is made.
Conclusion
HAIR-AN syndrome is an extreme form of PCOS. It is necessary to know how to evoke it in front of a clinical picture of severe hirsutism in the presence of acanthosis nigrigans.

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P442

Do we know how to supplement selenium in pregnancy to provide a proper micronutrient status for mother-newborn pairs?

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Background
Selenium (Se) sufficiency is beneficial for thyroid metabolism and pregnancy course due to its antioxidant and anti-inflammatory properties. As a part of selenoenzymes, it ameliorates autoimmune thyroid disease (AITD) progression in mothers and provides proper neurogenesis in fetuses. Despite lacking or conflicting recommendations for its supplementation in pregnancy, Se is used in a clinical setting, as a common constituent of multivitamin pregnancy diet supplements.
Objectives
The aim of the study was to evaluate Se supply and real-life supplementation effectiveness in pregnancy, based on Se biomarkers assessment in mothers and their newborns.
Methods
115 mother-child pairs were recruited at term delivery from obstetric department in one Polish centre. By the medical interview Se supplementation during pregnancy was assessed. The blood was collected before childbirth in mothers and during the third phase of delivery from the newborns' cord blood. Se status was assessed by measuring serum Se with Total Reflection X-ray Fluorescence analysis (on TXRF spectrometer S4 T-STAR) and selenoprotein P (SELENOP) with colorimetric enzyme immunoassay (selenOtest) concentrations and glutathione peroxidase 3 (GPX3) activity with a coupled enzymatic assay with t-butyl hydroperoxide as a substrate. This research was funded by National Science Centre in Poland (2019/33/N/NZ5/02303) as PRELUDIUM-17 grant.
Results
Se intake was declared by 30% of women, using multi-micronutrient supplements, with a mean Se dosage ($\pm$ SD) of 42 $\pm$ 14 µg/day. The whole group was deficient in Se in 89% (Se < 70 µg/l) and SELENOP in 77%. Median serum Se (54 vs. 58 µg/l), SELENOP (2.2 vs. 2.3 mg/l), or GPX3 (199 vs. 208.5 U/l) concentrations were slightly but not significantly higher in the supplemented than non-supplemented group. However, in the subgroups of low (< 55 µg/day) and moderate ($\geq$ 55 µg/day) daily Se dosage, median SELENOP was significantly higher in the latter group (1.84 vs. 3.17 mg/l, $P=0.006$).

Additionally, positive correlations of Se ($r=0.4$, $P<0.001$) within mother-newborn pairs and SELENOP ($r=0.78$, $P<0.001$; $r=0.72$, $P<0.001$), GPX3 ($r=0.78$, $P<0.001$; $r=0.53$, $P<0.001$) with Se between mothers and newborns adequately was observed.

Conclusions

Se supplementation from pregnancy multivitamin formulas was ineffective in the presented cohort. The mothers' Se supply reflects Se bioavailability for newborns. Considering diversity in geographical Se stores, differences in diet and individual Se level, no common guidelines can be applied worldwide, thus, there is a need of local Se status verification and adjusted recommendations.

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P443

Protein kinase B (Akt) blockade inhibits LH/hCG-mediated 17,20-lyase, but not 17α-hydroxylase activity of CYP17a1 in mouse Leydig cell steroidogenesis

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Androgens are sex steroid hormones fundamental for human reproduction. In males, they are produced upon luteinizing hormone (LH) action through its specific receptor (LHCGR) expressed in Leydig cells, supporting spermatogenesis. The human chorionic gonadotropin (hCG), acting on the same receptor but not expressed in men, is administered to improve testosterone synthesis in specific pathological contexts, such as hypogonadotropic hypogonadism and cryptorchidism. *In vitro* studies demonstrated that LHCGR mediates hormone-specific signaling patterns. In particular, LH mediates survival events in human ovarian cells, specifically induced via protein kinase B (AKT) phosphorylation, while hCG is relatively weak in inducing the same effect. We investigated the role of protein kinase B (Akt) in the modulation of Δ4 steroidogenic enzymes' activity, in the mouse Leydig tumor cell line (mLTC1). Cells were treated for 0-24 h with the 3-times 50% effective concentration of LH and hCG, in the presence and in the absence of the specific Akt inhibitor 3CAI. Cell signaling analysis was performed by bioluminescence resonance energy transfer (BRET) and Western blotting, while the expression of key target genes was investigated by real-time PCR. The synthesis of progesterone, 17α-hydroxy (OH)-progesterone and testosterone was measured by immunoassay. Control experiments for cell viability and caspase 3 activation were performed as well. We found that both hormones activated cAMP and downstream effectors, such as extracellularly-regulated kinase 1/2 (Erk1/2) and cAMP response element-binding protein (Creb), as well as Akt, and the transcription of *Stard1*, *Hsd3b2*, *Cyp17a1* and *Hsd17b3* genes, boosting the Δ4 steroidogenic pathway. Interestingly, Akt blockade decreased selectively *Cyp17a1* expression levels, inhibiting its 17,20-lyase, but not the 17-hydroxylase activity (Kruskal Wallis test and Dunn's post-test; $P<0.05$; $n=9$). This effect is consistent with lower Cyp17a1 affinity to 17α-OH-progesterone than progesterone. As a result, cell treatment with 3CAI resulted in 17α-OH-progesterone accumulation at 16-24 h and decreased testosterone levels after 24 h (two-way ANOVA and Bonferroni post-test; $P<0.05$, $n=16$). In conclusion, in the mouse Leydig cell line mLCT1, we found substantial Akt dependence of the 17,20-lyase activity and testosterone synthesis. Our results indicate that different intracellular pathways modulate selectively the dual activity of Cyp17a1.

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P444

Gender Affirming Hormonal Treatment (GAHT) and Demographics of Slovenian Transgender Adults

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Introduction

The number of individuals seeking gender-affirming hormonal treatment (GAHT), as well as the ratio between transgender men and transgender women, has increased over the past two decades. The type of GAHT varies significantly among different countries due to differences in availability and reimbursement policies. We aimed to analyze the kinds of GAHT and demographic characteristics of transgender adults at our endocrine clinic, the only center caring for transgender adults in Slovenia.

Methods

A retrospective analysis of the baseline demographic characteristics and GAHT type of transgender adults at our endocrine clinic from 2016 to 2022 was performed.

Results

From January 2016 until December 2022, 141 transgender adults (66 transgender women and 75 transgender men) were examined at our clinic. Transgender men were significantly younger at their first visit, with average age of 24.11 (6.51) vs. 31.35 (10.34) years for transgender women; $P<0.01$. The baseline BMI did not differ significantly between the two groups: for transgender men, BMI was 23.96 (5.61) kg/m^2 vs. transgender women 23.25 (4.24) kg/m^2. Transgender men use transdermal testosterone in 25% and depo testosterone undecanoate in 52%. We have lost follow-up for 10%, and 13% haven't started with testosterone therapy yet. Transgender women use anti-androgen treatment in 53% (25% have already had gender-affirming surgery, 10% haven't started with treatment yet, we have lost follow-up for 8%, and 6% refuse to use antiandrogen therapy). Half (54%) use cyproterone acetate, 42% spironolactone, and only one uses GnRH agonist. As for estrogen therapy, 56% of transgender women use peroral estradiol, 31% transdermal estradiol, and 13% intramuscular estradiol valerate.

Conclusion

Our analysis shows a slight predominance of transgender men receiving GAHT in Slovenia. They are significantly younger than transgender women when they first seek GAHT. At baseline, transgender men do not differ in BMI from transgender women. More than half of transgender men use intramuscular depo testosterone. About the same number of transgender women use cyproterone acetate and spironolactone as antiandrogen therapy. Over half of transgender women use peroral estradiol, and about a third use transdermal estradiol. So far, only a minority use intramuscular estradiol valerate.

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P445

Auto-immune diseases in Turner syndrome

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Introduction

Turner syndrome (TS) is a genetic disease, attributable to the total or partial loss of an X chromosome. The classic phenotype encompasses short stature, hypergonadotropic hypogonadism and dysmorphic features. It's also associated with other conditions such as autoimmune (AI) diseases.

Aim

Herein we aim to determine the frequency of AI diseases in TS and to identify the genetic variants of TS mostly associated with this latter condition.

Methods

We conducted a retrospective descriptive study. We collected the medical records of patients who had a turner syndrome and consulted our Endocrinology department at the Hedi Chaker University Hospital in Sfax, Tunisia, between 1990 and 2021. We included patients who had the cytogenetic confirmation of TS.

Results

The total number of our patients was 45. The mean age of diagnosis was 16 years with extremities varying from 3 months to 44 years. The majority of our patients were diagnosed between the age of 14 and 20 years (44. 2%). The most frequent karyotype among the patients with TS was X monosomy (49%). Mosaic forms without structural abnormalities of the X chromosome were found in 31 % whereas mosaic karyotype with structural abnormalities represented only 20 %. A total of 11 patients had auto immune diseases (24.4%), predominantly represented by disorders of thyroid gland (72.2 %). In fact, seven patients had hypothyroidism while only one had hyperthyroidism related to Graves' disease. The other AI diseases identified in our cohort were: alopecia areata, rheumatoid arthritis, Behcet disease and psoriasis, found in one case each. AI diseases were mostly seen in patients with monosomy of X: 22.4% vs 17.4% in mosaic forms ($P=0,72$). Particularly, it was the mosaic variants with structural abnormalities of the X chromosome who were prone to develop AI conditions when comparing it with those without structural variants of the X chromosome: 20% vs 15.4%.

Conclusion

Patients with TS are prone to develop AI conditions as demonstrated by our study and thus a systematic clinical as well as biological screening oh these conditions should be conducted at least on an annual basis.

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P446

Delineating molecular mechanisms involved in hypo- and hyper-prolactinemia affecting male fertility

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The endocrine system is crucial in spermatogenesis and any hormonal alterations may affect fertility. Prolactin (Prl) plays a role in male reproduction, as evidenced by presence of prolactin receptors on various testicular cells. However, the exact mechanism and physiological role of testicular prolactin receptor during spermatogenesis remains elusive. Clinical conditions such as hyper- and hypo-prolactinemia are known to have deleterious effects on male reproduction. The aim of this study is to delineate the mechanisms by which hyper- and hypo-Prl affects male fertility. *In vivo* male rat model for hyper- and hypo-Prl was established using dopamine receptor antagonist (Fluphenazine) and agonist (Bromocriptine), respectively. Treatment with fluphenazine (hyper-Prl) and bromocriptine (hypo-Prl) for 60 days results in a significant decrease in fertility as compared to control male rats. This subfertility was due to an increase in pre- and post-implantation loss and a concomitant decrease in litter size when mated with control female rats. There was also a significant increase in the time taken for copulation after fluphenazine treatment. A significant reduction in sperm counts was observed in both the treatments. Sperm motility was found to be reduced significantly in hyper-Prl. Hormonal analysis revealed that LH, FSH, testosterone, and estrogen are significantly decreased in hyper-Prl group. In hypo-Prl group, LH and FSH were significantly increased, whereas testosterone and estrogen remained unaffected. Further, analysis of differential germ cell population by flow cytometry revealed that hyper-Prl group showed significant reduction in elongated and elongating spermatids and a concomitant increase in round spermatids indicating an arrest in differentiation of round to elongated spermatids. Additionally, these findings were confirmed by expression of cell-type specific markers by qPCR. To further delineate the molecular mechanisms underlying hyper-Prl v/s hypo-Prl, transcriptome analysis to study testicular gene expression was carried out. Differentially expressed genes obtained were subjected to gene ontology, pathway analysis, and enrichment map analysis. In conclusion, the results of this study demonstrate that altered levels of prolactin can have deleterious effects on different aspects of male fertility. It also suggests that the detrimental effects of hyper-Prl are more profound than hypo-Prl. Hyperprolactinemia could be one of the factors of idiopathic male infertility and routine screening of prolactin levels in infertile males should be recommended.

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P447

Influence of ovulation, anovulation and progestin on Phoenixin-20 and Nesfatin-1 in patients with polycystic ovary syndrome (PCOS)

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Polycystic Ovary Syndrome (PCOS) is the most common endocrinological dysfunction among women of reproductive age, often featuring hyperandrogenemia and anovulation. Reciprocal effects exist between elevated LH, androgens, anovulation and other features, increasing the hormonal disbalance, while the origins of PCOS are still not fully clear. The neuropeptides Phoenixin-20 (PNX20) and Nesfatin1 (NES1) are being co-expressed and thought to play opposing roles in the hypothalamic–pituitary–gonadal axis. PNX20 seems to regulate pituitary LH secretion and to be elevated in PCOS. NES1 is involved in metabolism and inflammation. This study characterized changes of PNX20 and NES1 within cycles of PCOS patients with anovulation, ovulation and progestin administration.

Methods

Women of reproductive age with PCOS, diagnosed according to the Rotterdam Criteria were included in this observational study after informed consent. All women had a clinical indication for a progestin test, conducted with 10 mg dydrogesterone daily for 14 days in the second half of the first menstrual cycle. For observational purposes 5 blood samples were taken from each participant, on day 3 - 7 of the menstrual cycle and 14 - 19 days later, spanning two and a half consecutive menstrual cycles – one under dydrogesterone and 1.5 cycles thereafter. Follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, testosterone, dehydroepiandrosterone-sulfate (DHEAS), prolactin, and sexual hormone binding globulin (SHBG) were measured.

Results

40 complete cycles in 26 patients were analyzed. 20 cycles were anovulatory, 20 ovulatory-marked by a progesterone increase over 5.8 ng/ml. A linear association was found between PNX20 and LH levels and significant ($P<0.05$) differences in anovulatory cycles were noted between follicular phase (mean PNX20 = 1.89 ng/ml ± 1.16 ng/ml) and the second half of the cycle (mean PNX20 = 2.90 ng/ml ± 1.52 ng/ml). Pearson's coefficient between progesterone and PNX20 was -0.551 ($P<0.05$). In the follicular and luteal phase of ovulatory cycles, the difference was not significant. By contrast, NES1 levels only differed significantly between phases of ovulatory cycles (mean follicular NES1 = 1.83 ng/ml ± 1.20 ng/ml, mean luteal NES1= 2.16 ng/ml ± 1.22 ng/ml). Exogenous progestin administration at the dose administered had no significant influence on PNX20 or NES1 levels. We conclude that endogenous progesterone and/or ovulation itself may be important modulators of PNX20 and NES1. This opens different explanation models as to why PNX20 is elevated amongst PCOS patients.

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P448

Persistent effects of anabolic, androgenic steroids on muscle mass and strengths years after cessation?

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Objective

The use of anabolic, androgenic steroids (AAS) to increase muscle mass and strength has become widespread among younger men engaged in recreational strength training. Although, repercussions exist for elite athletes with a ban of two to four years, the long-term effects on muscle mass following cessation are currently unknown. The present study aims to investigate previous users' ability to retain lean mass and strength after long-term AAS cessation.

Design and methods

A cross-sectional study of men involved in strength training, including current and previous users of AAS, and recreational athletes with no prior use of AAS (controls). Lean body mass was assessed by dual-energy X-ray absorptiometry (DXA). Strength was assessed by one repetition max (1RM) bench press and leg press performed under controlled laboratory settings. Standardized questionnaires were used to assess AAS use, and blood was drawn, measuring serum total and free testosterone using liquid chromatography mass spectrometry.

Results

We included 40 participants (14 current, 11 previous, and 15 controls with no AAS use). The mean (SD) age was 31.3 (6.8) years, with no differences between groups (0.920). The median (IQR) length of AAS use was 149.5 (104-208) vs. 48 (24-186) weeks for current and previous users ($P=0.049$). Median (IQR) time since cessation was 5.0 (1-14) years among previous users. As expected, free testosterone levels were increased in current AAS users ($P=0.017$), while no difference was observed among previous users ($P=0.332$) and controls (median (IQR): 1.7 (0.5-3.1) vs. 0.4 (0.4-0.5) vs 0.6 (0.5-0.7) nmol/l). Interestingly, lean mass of the upper extremities was higher in both current ($P=0.010$) and previous users ($P=0.021$) compared with controls (12.4 vs. 12.3 vs. 10.8 kg). In contrast, no difference in lean mass was observed for the lower extremities ($P=0.200$). Strength performance in 1RM leg press was significantly higher in current users ($P=0.015$), while a benefit was suggested in previous users ($P=0.068$) as compared with controls (367 vs. 279 vs. 235 kg). Accordingly, current, and previous users showed a tendency towards outperforming controls in 1RM bench press with (133 vs. 136 vs. 111 kg)($P<0.010$).

Conclusion

Previous users showed compartmentally increased lean body mass and a tendency towards greater strength even 5 years after discontinuation of AAS when compared with controls, mirroring findings among current users. The suggested ability to retain an increase in lean mass following AAS use may translate to retaining an advantage in competitive settings.

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P449

Maternal cortisol levels in 3rd trimester and early language development, a study of 1,093 mother-child pairs from Odense Child Cohort

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Background
Language development during early childhood is considered an important marker of fetal neurodevelopment. Prenatal cortisol exposure plays a critical role in maturation of the fetal brain; however, the effect on offspring language development needs further investigation. This study aimed to evaluate the association between maternal 3rd trimester cortisol and early longitudinal offspring language development and to test whether there was sex differences in the association.
Design
Prospective observational study.
Setting
Odense Child Cohort.
Patients
The study cohort included 1,093 mother-child dyads (570 boys and 523 girls).
Intervention
Fasting morning serum (s-) cortisol was collected from 3rd trimester (gestational week 26-28) pregnant women and measured by liquid chromatography–tandem mass spectrometry.
Main Outcome Measures
Offspring receptive and productive vocabulary assessments by MacArthur-Bates Communicative Development Inventories parent reports were completed every third month from child age 12 to 37 months.
Results
Levels of cortisol were higher in women carrying a girl (858 $\pm$ 214 nmol/l) than in women carrying a boy (820 $\pm$ 222 nmol/l). Higher 3rd trimester maternal cortisol levels showed a positive association with development of productive vocabulary in boys at age 12-21 months ($OR = 1.23$, $SE = 0.07$, $P = .005$) and age 22-37 months ($OR = 1.09$, $SE = 0.06$, $P = .967$). Higher maternal cortisol levels in 3rd trimester were positively associated with receptive vocabulary in girls at 12-21 months-of-age ($OR = 1.16$, $SE = 0.05$, $P = .002$).
Conclusions
Maternal 3rd trimester s-cortisol levels were positively associated with early language development in children age 12-37 months.
Funding
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P450

Cardiovascular Events and Gender-Affirming Hormone Therapy, 10 Years of Follow-Up

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Objectives
Most transgender persons (0.3-0.5% of total population) are under gender-affirming hormone therapy (GAHT). Several studies have reported an increased morbimortality due to cardiovascular events (CVE), infectious disease and suicide. However, these studies were made on small populations and short follow up. We evaluated the changes on anthropometric variables, risk factors for cardiovascular diseases (CVD) and CVE at 5 and 10 years of follow up in a transgender population followed in a Gender Identity Unit in Catalonia.
Methods
Retrospective longitudinal study including transgender people visited at the Hospital Clinic of Barcelona between 2006 and 2010. Anthropometric variables, analytical parameters, clinical data on hypertension, diabetes, dyslipidemia, thrombotic events (deep venous thrombosis (DVP) and pulmonary embolism), cerebrovascular events (stroke or transient vascular accident) and ischemic heart disease (heart attack, stable and unstable angina) were collected at baseline, 5 and 10 years together with the GAHT schedule. The events were compared with the Spanish ciswomen and cismen population age adjusted.
Results
248 transgender people were included, 60.9% transwomen (32.6$\pm$10.0y) and 39.1% transmen (28.8$\pm$8.4y). At 5- and 10- years follow-up body mass index, total cholesterol and LDL levels increased in both transmen and transwomen as well as triglycerides in transmen; $P<0.01$. Hypertension increased in transwomen and transmen at 10 years ($P<0.01$ and $P=0.02$, respectively). During follow-up, two DVTs, two ischemic events, and two strokes were reported in transwomen, with an incidence rate of 0.33 %-year (ciswomen, age range 27-60: 0.22%-year; cismen, age range 27-60: 0.36 %-year); one DVT was reported in transmen, an incidence rate of 0.10%- year (cismen, age range 27-35: 0.07 %-year; ciswomen, age range 27-35: 0.05%-year). Obesity was associated to cyproterone acetate in transwoman; and hypertension and dyslipidemia were associated to testosterone treatment. No person died.
Conclusion
These data suggest that there is a small increased risk of CVE in transwomen in comparison to ciswomen and no difference with cismen. In transmen, small increased risk of CVE in comparison to ciswomen was observed. However, no association was found with the regimen of GATH and low number of events and small population should be considered. Toxic habits are highly prevalent in our population (42% of transwomen and 60 % transmen in comparison with 16.4% of ciswomen and 23.3% of cismen in Spanish population). Recommendation of healthy lifestyle habits should be made. There are no previous data regarding CVE at 10 years of follow up in Spanish trans population.

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P451

Dysfunction of Estrogen Signaling as a Novel Molecular Signature of PolyCystic Ovary Syndrome

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Estradiol (E2) plays an essential role in woman fertility. E2, locally produced by granulosa cells (GCs) of ovarian antral follicles, controls follicular development and selection, and triggers the gonadotropin surge that leads to ovulation. Dysovulation arising from the arrest of antral follicle growth and maturation occurs in up to 10 % of reproductive-aged women suffering polycystic ovary syndrome (PCOS). Although the diagnostic criteria for PCOS are clearly established, the molecular etiology of this syndrome is still under debate. Given the high importance of E2 in follicular growth and selection, our study aimed at identifying the possible disturbances of E2 signaling, predominantly mediated by estrogen receptors ERα and ERβ, that could impact GCs steroidogenic function and participate in PCOS. For this purpose, we performed primary cultures of GCs from follicles of 30 patients undergoing *in vitro* fertilization either for male factor infertility (control) or for PCOS. First, we analyzed by RT-qPCR the expression level of the two transcription factors ERα and ERβ in GCs, and demonstrated that they exhibited the same level of expression in control and PCOS patients. Strikingly, E2 treatment significantly regulated the expression of genes involved in various biological processes (*steroid biosynthesis: Cyp19a1 and Cyp11A1; cell survival: Bcl-2*) in primary cultures of control GCs, whereas in PCOS cells, E2 was ineffective despite the presence of ERα and ERβ. Then, we characterized the steroidogenic activity of GCs from control and PCOS, by measuring steroid hormone concentrations in both cells and follicular fluids (FF) using GC/MS. Our analyses demonstrated that E2, pregnenolone (P5) and progesterone (P4) concentrations were significantly lower (by 27 %, 41 % and 45 % respectively) in PCOS FF when compared to control. They also revealed that contrary to P5, the reduction of concentrations of E2 and P4 in FF did not correlate with a decrease in their intracellular biosynthesis. Indeed, intracellular concentrations of E2 and P4 were similar in both groups, whereas that of P5 was significantly reduced (by 59 %) in PCOS, probably through the down-regulation of *Cyp11A1* expression that we observed. Altogether, our study provides a novel signature of PCOS by revealing an impairment in E2 signaling that may contribute to follicular growth

dysregulations. In addition, our results suggest the existence of a selective steroid degradation in FF of PCOS patients that may explain lower levels of anti-inflammatory steroids P4 and P5, and enhance the local ovarian inflammation contributing to unsuccessful oocyte maturation.

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P452

The relationship between steroidogenesis and healthy eating index in polycystic ovary syndrome

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Aim
We aimed to examine the relationship between the healthy eating index (HEI) and steroidogenesis in polycystic ovary syndrome (PCOS) patients and healthy controls.
Materials and Methods
In addition to demographic records and routine biochemical tests, HEI was calculated from three-day nutritional records in the Bebis program. Adrenal steroidogenesis panel was measured by LCMS.
Results
The study included 50 women with PCOS and 42 healthy controls. The groups were matched in terms of age and BMI. Waist circumference and hip circumference were significantly higher in the patient group. Although there was no difference in terms of fasting blood glucose and hba1c, HOMA IR was statistically significantly higher in favor of the patient group. However, there was no difference between the groups in terms of HEI. In the steroidogenesis hormone panel, only total testosterone, dheas and 17OHP and 11 deoxycorticosterone were statistically different in favor of the PCOS group. There was a positive relationship between HEI and 11 deoxycortisol in the PCOS group, while a negative relationship was found in the control group. On the other hand, while there was a negative relationship between HEI and pregnenolone in the PCOS group, no relationship was found in the control group. The rest showed no correlation with HEI scores in either group.
Conclusions
Although PCOS patients have similar weight and nutrition patterns to healthy controls, they may have metabolic dysfunction. A healthy eating pattern may be likely to shift the axis of andogenesis to the side of the cortisol axis. Nutrition can play a major role in the management of these patients.

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P453

In between isolated premature thelarche and central precocious puberty: when DHEAS makes the difference

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Background
Precocious puberty (PP) in girls is most frequently an idiopathic gonadotropin-releasing hormone (GnRH)-dependent PP, being thelarche the typical first sign. It is well established that increased dehydroepiandrosterone sulphate (DHEAS) levels are associated with premature adrenarche and may characterize PP too. However, its relationship with signs of hypothalamic-pituitary-gonadal (HPG) axis activation and oestrogen exposure is still to be elucidated.
Aims
Assessing the association between DHEAS levels and other parameters of HPG activation in girls with precocious thelarche.
Methods
At this aim, 60 girls (median chronological age-CA 7.8 years, range IQ 7.0-8.3) referring to our Endocrine Clinic for suspected PP were consecutively enrolled. In all patients the following data were collected: basal and stimulated (GnRH test at 2.5 mg/kg) LH and FSH levels, basal ACTH, cortisol, DHEAS, androstenedione, testosterone, 17-α hydroxyprogesterone, 17-βoestradiol levels, pelvic ultrasound (US) and hand and wrist X-ray for bone age (BA) assessment.
Results
Median DHEAS values were 506 mg/l (range IQ 265-872), 0.77 SDS (range IQ -0.72-2.15), being >2 SDS in 19/60 patients. In all patients, other adrenal function tests were in the normal range. Out of 60 girls, 27 showed a pre-pubertal response to GnRH test (LH <5 mIU/l). Higher DHEAS levels were found in this group vs girls with pubertal LH peak (2.07 SDS, range IQ 0.09-2.76 SDS vs -0.07 SDS, range IQ -0.87-1.28 SDS, $P=0.004$). At logistic regression DHEAS SDS was negatively associated with LH response to GnRH test ($P=0.006$). Similarly, at multiple regression, DHEAS values were negatively associated with LH peak ($P=0.04$) and oestradiol levels ($P=0.04$). Patients with elevated DHEAS concentrations showed higher levels of testosterone ($P=0.04$) and androstenedione ($P=0.02$). No other differences were found between the two groups regarding clinical presentation, pelvic US and BA.
Conclusion
In the presence of signs of HPG axis activation and oestrogen exposure, pubertal GnRH test response confirms PP. Our data suggest that elevated DHEAS concentrations, in the absence of HPG axis activation, may drive estrogenization signs. Indeed, an oestrogen receptor concentration-dependent transactivity action of DHEAS has already been described in *in vitro* studies. Moreover, this condition can be different from a mere normal variant of PP thus requiring an appropriate follow-up and eventual therapeutic approach. Further studies are needed to support our findings and to insight into their impact in patients' management.

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P454

Effect of selective oestrogen receptor modulators/aromatase inhibitors on semen parameters in men with secondary hypogonadism; systematic review and meta-analysis

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Introduction
Selective oestrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) potentially increase endogenous gonadotrophin and testosterone secretion in men. They are used off-label in men with hypogonadism and/or infertility. There is a lack of guidance on using these agents in men with secondary hypogonadism, though these agents are widely used in these people as a cheaper alternative to gonadotrophins.
Methods
Systematic search was conducted in PubMed, MEDLINE, Cochrane library and ClinicalTrials.gov for randomised controlled trials (RCTs) and non-randomised studies of intervention (NRSI) reporting SERM and/or AI effects on semen parameters or fertility in men with secondary hypogonadism (PROSPERO-CRD42022306535). Study selection and data extraction were performed by two reviewers independently. The risk of bias (ROB) was assessed using ROB-2 and ROBINS-I tools. Results of RCTs were summarised using vote counting while summarising effect estimates where available. NRSI meta-analysis was conducted using the random-effect model. Certainty of evidence was assessed using GRADE.
Results
Five NRSIs ($n=105$) of SERMs showed an increase in sperm concentration [pooled mean difference 6.64 million/ml; 95% CI 1.54, 11.74] and three NRSIs ($n=3$) of SERMs showed an increase in total motile sperm count [pooled mean difference 10.52; 95% CI 1.46-19.59], with very low certainty of evidence due to critical ROB. All participants had infertility, however, the aetiology of hypogonadism was not specified in four studies and the mean BMI of participants in those studies was >30 kg/m^2. All three RCTs ($n=275$) comparing SERMs to testosterone gel showed the benefit of SERMs on sperm concentration. Four RCTs ($n=591$) comparing SERMs to placebo showed a heterogeneous effect on

sperm concentration. Three RCTs included men with overweight/obesity, whereas participants in the other studies also had a mean BMI >28 kg/m^2. Results were of very low/low certainty of evidence due to the high ROB. Limited pregnancy or live birth data were available. No AI data on sperm parameters or fertility compared placebo or testosterone were found. Single cases of fatal stroke and venous thromboembolism were associated with SERMs and AIs, respectively; however, no causality could be established.
Conclusions
Current studies are of limited size and quality but suggest that SERMs may improve semen quality in men having low testosterone with low/normal gonadotrophins, particularly when associated with obesity. Well-designed, randomised studies recruiting men with a clear diagnosis of secondary hypogonadism are needed to determine whether SERMs improve spermatogenesis and live-birth rates in couples affected by secondary hypogonadism.

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P455

Decreased Quality of Life in Previous Users of Anabolic Androgenic Steroids Years After Cessation

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Background and Aim
Use of anabolic androgenic steroids (AAS) has moved from elite sports to the broader population. Studies suggest that AAS cessation is often associated with immediate various AAS withdrawal and hypogonadal symptoms. Quality of life using a standardized questionnaire has never been assessed in AAS users. The Short-Form 36 (SF-36) questionnaire is a highly validated and used instrument for assessment of quality of life. The questionnaire consists of a total eight subcategories divided into four physical health categories and four mental health categories. The objective of this study was to assess quality of life in current and previous illicit AAS users compared with healthy control participants who had never used AAS.
Methods
Community-based cross-sectional study including men involved in recreational strength training. SF-36 questionnaire was completed, history of AAS use was obtained using a standardized questionnaire and blood was drawn for measurement of serum total testosterone using liquid chromatography mass spectrometry.
Results
We included 89 current and 61 former AAS users and 30 healthy age-matched never users, as controls. The mean (SD) age of all participants was 34 (8) years. Accumulated duration of AAS use, was 163 (127;208) weeks among current users and 104 (78;138) weeks among former users, (P= 0.019). Duration since AAS cessation, was 50 (33;68) months and 45 (74%) former AAS users discontinued AAS use more than one year prior to inclusion. Previous AAS users displayed impaired quality of life on all eight SF-36 subcategories compared with the never users (P<0.001). Ongoing AAS users perceived their general health as impaired and displayed decreased social functioning compared with healthy controls (P<0.05), while quality of life did not differ between the two groups with respect to the other six categories. Mean (SD) serum testosterone was lower in previous AAS users 14 (6) nmol/l compared with healthy controls 19 (5) nmol/l (P=0,0002). In age-adjusted analyses of covariance, among former AAS users and non-AAS users, lower serum total testosterone levels were associated with impaired quality of life in all SF-36 subcategories, except bodily pain (P<0.05). The SF-36 score were not associated with accumulated duration of AAS use among current and former AAS users.
Conclusions
Previous AAS users exhibited impaired quality of life on all physical and mental health parameters years after AAS discontinuation, which may be related to lower serum testosterone levels in this group compared with non-users.

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P456

Nurse-Led Care for Transgender and Gender Diverse Individuals: A Cross-Sectional Study of International Context and Practice

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Introduction
Gender minorities, including transgender and gender diverse (TGD) individuals face health disparities and significant barriers in accessing healthcare. Lack of access to providers knowledgeable in TGD health needs is the single greatest barrier to care. Existing literature on TGD care has almost exclusively focused on physicians and there is scant literature on the role of nurses. We aimed to describe exemplars of nurse-led TGD care internationally to better understand the structure, process, and outcomes of nurse-led TGD care as well as recommended best practices nurse-led TGD care.
Methods
This descriptive cross-sectional study used a convenience sample of nurse-led TGD clinics drawn from international endocrine nursing organizations. Identified clinics completed an online survey based on the Donabedian Model of quality care (structure, process, outcome). 'Structure' included a description of health system, guidelines used by the clinic, team composition/organization, and contextual medico-legal issues. Process assessed nursing roles/activities and perceived promoters/barriers to TGD care. Outcomes were assessed by identifying metrics employed by the clinics. Two independent investigators reviewed survey responses and collated descriptive findings in tables, used thematic analysis to identify salient features and themes, and validated the synthesis with respondents.
Results
Five established TGD clinics were identified from the United States (n=3), United Kingdom, and Sweden. Clinics were government funded (n=2), based within academic medical centers (n=2), and a free-standing community practice. Respondents included both registered nurses and advance practice nurses (nurse practitioners/nurse prescribers) who provide pediatric (n=2), adult (n=1), and care across the lifespan (n=2). Common 'structure' elements included: creating a welcoming environment, interprofessional team, and use of clinical guidelines. The 'process' of care was characterized by: commitment to a gender-affirming philosophy and person-centered care, emphasis on collaborative care/team communication, and dedicated time for case management. Few outcomes were measured (primarily client census). All clinics noted the importance of access to care, training clinicians/staff, and structured data collection methods as promoters of high-quality TGD care.
Discussion
Findings suggest nurses play an important role in increasing access to gender-affirming and person-centered care. Nursing care emphasizes interprofessional collaboration, health promotion, empowerment, and patient advocacy. We identify promoters and best practices based on expert opinion - yet more work is needed to establish evidence-based practices and nurse-sensitive outcome measures for TGD care.

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P457

Evaluation of Oxidative Stress Parameters and Serum Fetuin-A Levels in Patients with Polycystic Over Syndrome

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Introduction
Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism, oligo-anovulation and/or polycystic ovary. Hypotheses such as genetic and environmental causes, disruption of the hypothalamo-pituitary-gonadal axis, insulin resistance, hyperinsulinemia and increased oxidative stress have been proposed to explain the etiopathogenesis of PCOS. In our study, we aimed to evaluate oxidative stress parameters and serum fetuin-A levels and to investigate their role in PCOS.
Materials and Methods
32 PCOS patients aged 18-40 years and 25 women without any known systemic disease were included in the study. After their systemic examination, body weights and heights were measured. In the first 3 days of their menstruation, following 8-10 h of fasting, a morning blood sample is taken and hormone profile

(FSH, LH, estradiol, progesterone, testosterone, DHEA-S, 17-hydroxyprogesterone, TSH, fT4), lipid profile (total cholesterol, HDL, LDL, TG), fasting glucose, HbA1c, insulin, liver and kidney function tests were studied. To investigate the role of oxidative stress in PCOS, the levels of oxidant substances Malondialdehyde (MDA), 4-hydroxynonenal (4HNE), peroxynitrite and Nuclear factor erythroid 2 (NRF2), which is considered as an indicator of the antioxidant system, were measured. Serum Fetuin-A levels were measured.
Results
It was shown that there was no statistically significant difference between the groups in terms of mean age, height, weight and body mass index. Insulin, fasting glucose, HbA1c levels and HOMA-IR values were found to be significantly higher in the PCOS group ($P=0.001$, $P=0.001$, $P=0.001$, $P=0.034$, respectively). Fetuin-A level did not differ significantly in both groups ($P=0.342$). Total cholesterol, HDL and triglyceride levels were found to be significantly higher in the PCOS group ($P=0.001$, $P=0.004$, $P=0.001$, respectively). MDA and 4HNE levels were found to be significantly higher in the PCOS group ($P=0.001$, $P=0.001$, respectively). Peroxynitrite levels were higher in all patients in the PCOS group, but there was no statistically significant difference between the groups ($P=0.546$). NRF2 levels was found to be significantly lower in the PCOS group ($P=0.018$).
Conclusion
In our study, PCOS was found to be associated with insulin resistance and dyslipidemia. This may pose a risk factor for metabolic complications and cardiovascular diseases. The fact that there was no significant difference between the groups in terms of fetuin-A levels indicates that additional studies are needed on the relationship between fetuin-A and insulin resistance. The fact that oxidative stress markers are high and antioxidant metabolites are low in PCOS patients may contribute to the determination of new strategies in the follow-up and treatment of long-term metabolic complications of this syndrome.

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P458

Association between androgen levels and SPISE index in patients with polycystic ovarian syndrome

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Introduction
Polycystic ovarian syndrome (PCOS) is characterized by hyperandrogenism, chronic oligo-/anovulation and polycystic ovarian morphology. Hyperandrogenism is a key diagnostic feature of PCOS and according to ESHRE/ASRM criteria it can be clinical and/or biochemical. SPISE index (single-point insulin sensitivity estimator index) is a new indicator of insulin sensitivity and a predictor of abnormal glucose metabolism. The aim of the research was to analyse association between SPISE index and androgenic disorders which are highly prevalent in PCOS.
Subjects and methods
We analysed 145 female patients with PCOS diagnosed using ESHRE/ASRM criteria and with exclusion of relevant diseases. Patients were divided according to age into two groups, $\leq$ 30 years (PCOS A, n: 74, age: 23.3 ± 3.1 years, body mass index (BMI): 23.1 ± 4.4 kg/m^2) and >30 years old (PCOS B, n: 71, age: 35.6 ± 4.9 years, BMI: 25.3 ± 6.3 kg/m^2). We measured serum levels of total cholesterol, LDL and HDL cholesterol, triglycerides, total testosterone, SHBG, DHEA-S, androstenedione and 17OH-progesterone, while values of free androgen index (FAI) and SPISE index were calculated using appropriate formulas. Statistical analysis was performed using the SPSS software.
Results
The two groups did not differ in BMI (23.3 ± 4.4 vs. 25.3 ± 6.3 kg/m^2, $P=0.126$), waist circumference (77.0 ± 12.9 vs. 82.0 ± 15.2 cm, $P=0.071$) and total testosterone levels (2.0 ± 1.0 vs. 1.9 ± 0.9 nmol/l, $P=0.332$). SPISE index was lower in PCOS B group (PCOS A:PCOS B: 8.7 ± 2.6 vs.7.6 ± 2.6, $P=0.022$). There was a statistically significant higher value of SHBG in B group (PCOS A:PCOS B: 44.0 ± 30.7 vs. 48.2 ± 17.1 nmol/l, $P=0.037$), but there was no difference in FAI ($P=0.291$). The SPISE index positively correlated with SHBG levels in both groups of patients (PCOS A: $P=0.006$, PCOS B: $P=0.001$), but negatively correlated with FAI in B group ($P=0.018$).
Conclusion
Hyperandrogenism in patients with PCOS is associated with poor metabolic outcome. Our analysis showed worsening of the SPISE index with age of our subjects, and its association with indicators of hyperandrogenism could predict metabolic events during the life of patients with PCOS.

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Improved self-reported confidence levels to manage transitional endocrine cases following Simulation via Instant Messaging – Birmingham Advance (SIMBA) training

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Introduction
Simulation via Instant Messaging – Birmingham Advance (SIMBA) is an online real-time simulation-based learning model which has proven to improve participants' confidence in managing simulated cases in various conditions. Transitional endocrinology is a unique set of conditions which not only needs clinical skills but also requires excellent team working and communication skills. The aim of the study was to assess the effectiveness of the SIMBA model in improving self-perceived clinician confidence in the management of transitional endocrinology cases.
Methods
The session was conducted on 4 November 2022 as a hybrid option where participants joined the session either in person or virtually. Four transitional endocrinology scenarios, focussing on Turner's syndrome, congenital adrenal hyperplasia, type 1 diabetes mellitus and type 2 diabetes mellitus, were simulated using participant-moderator interaction via Whatsapp. These scenarios were based on real-life cases, anonymised to maintain confidentiality. After conducting the simulated cases the content was discussed on Zoom by three expert chairs, each a specialist in various subspecialities of transitional endocrinology. During this discussion, participants interacted with chairs and fellow participants via chat option. Participants completed pre- and post-SIMBA surveys designed to evaluate self-perceived improvement in confidence and ACGME Core Competencies, and perceptions surrounding SIMBA. Responses were quantitatively analysed using the Wilcoxon Signed Rank test and answers to open ended questions were qualitatively assessed using a thematic analysis.
Results
20 participants completed both pre- and post- SIMBA surveys. Participant self-perceived confidence in the management of simulated topics increased following the session (pre- vs post-SIMBA survey: 31.3% to 91.3%, $P<.0001$). There was also an increase in confidence to manage non-simulated conditions which were included in the discussion (14.0% to 66.0%; $P<.0001$). However, the change was greater with simulated cases (simulated vs non-simulated: 60% vs 52%). Most participants reported an improvement in Core Competencies defined by Accredited Council of Graduate Medical Education (patient care, 95%; knowledge on patient management, 95%; practice-based learning, 90%; systems-based practice, 85%; professionalism, 80%). 95% rated the quality of SIMBA session as excellent or good. 85% of participants strongly agreed or agreed that the topics simulated were applicable to their practice and 90% would attend SIMBA sessions in the future.
Conclusion
SIMBA is an effective tool for improving clinician confidence in the management of transitional endocrine topics. Focus for future studies will be implementing SIMBA for larger groups of clinicians to determine the wider effectiveness of simulation-based learning for transitional endocrinology.

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P460

Prevalence of body dysmorphism in PCOS women

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Polycystic ovary syndrome (PCOS) is the most common reproductive problem in women of childbearing age attending an endocrine clinic with a reported prevalence of between 4-8 %. The classical symptoms result from excess ovarian androgen production and chronic anovulation. Ovarian ultrasound shows more than 10 follicles, 2-10mm in diameter. A common presentation in the clinic can be menstrual dysfunction but the most characteristic feature of the syndrome is the hirsutism which varies in severity and site. Hair growth on the face and chin can be quite extensive as can excessive hair loss on the head and frontal balding and acne all due to androgen excess. Obesity has also been reported in about half of PCOS patients. It is characterised by an increase in waist- to-hip ratio or android appearance as opposed to truncal obesity with an incidence of 7.5% of type 2 diabetes. It is well established that PCOS women suffer from impaired emotional well being and have a marked reduction in the quality of their life, as well as anxiety and depression. The role of physical appearance, obesity, and hirsutism have been well established as contributing to this reduced quality of life in studies done in USA but not to the same extent in the Middle East. The purpose of our study is to review the impact of PCOS on a cohort of young women attending an endocrine clinic in a tertiary referral teaching hospital in the Kingdom of Bahrain. We enrolled 40 PCOS women in a cross-sectional survey between the ages of 19 and 40 years to determine the severity and prevalence of body dysmorphism in our PCOS patients. We used a questioner of 30 questions which enquired about BMI, hair distribution, acne, menstrual cycle, and patients' perception of their bodies. Based on WHO classification of weight, 20% were of normal weight, 12.5 % overweight and 45% were obese. 66.6% had male pattern hair growth with 91.6 % having male pattern balding. 87.5% mentioned that their weight/body shape influenced in a negative way the way they saw themselves. Nevertheless 58.3 % felt that they were attractive. Finally, 90 % expressed the desire to lose weight, although they felt that minor weight gain did not influence how they saw themselves. In conclusion, the evidence in this study to date is that the main problem that influenced their perception of their body was their weight and not hirsutism.

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Extremely high testosterone level in a woman without virilization signs. Is it only laboratory pitfalls?

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Introduction
High androgen levels and infertility in reproductive women, beyond the most common cause of polycystic ovary syndrome (PCOS), is often a challenge diagnosis. Ovarian steroid cell tumor is considered a rare subtype of hormone-secreting ovarian tumor, accounting for about 0.1% of all ovarian tumors.
Aim
To report a case of extremely high testosterone levels in a woman with secondary amenorrhea but without signs of virilization, and describe diagnostic assessment of testosterone levels.
Methods
Assessing true testosterone levels by three different manufacture methods Centaur (Siemens), Cobas (Roche manufacture), Architect (Abbott manufacture), respectively and extraction procedure with diethyl ether prior to immunoassay.
Case Presentation
A 27 years old woman was followed for a presumed ovarian dermoid cyst and PCOS. Two years later hormonal treatment was stopped in intention for conceive, but menstruation did not resume. Evaluation revealed extremely high testosterone level of 22.1nmol/l, (reference value $<$2.1 nmol/l) measured by Centaur analyzer (Siemens manufacture) without signs of virilization. Levels of SHBG, FSH and LH were within the normal range. The sample was processed by two alternative methods, Cobas (Roche manufacture) and Architect (Abbott manufacture), showing similar results for testosterone: 19.5 and 23.0 nmol/l, respectively. The same values of total testosterone were found after heterophile and nonspecific antibodies blocking test. At this point, extraction procedure with diethyl ether was performed prior to immunoassay, then testosterone was measured on Cobas/Roche analyzer. A level of 5.6 nmol/l total testosterone was found after the extraction procedure. An abdominal contrast computed tomography scan (CT) confirmed a 30 mm X 36 mm round solid mass in the left ovary, not characteristic of a dermoid cyst. The ovarian mass was resected. Histological diagnosis reveled an ovarian steroid-cell tumor (SCT) not otherwise specified (NOS). Twenty-four h after the surgery total testosterone level returned to normal range, 0.6 nmol/l. A month after surgery the patient resumed menstruation.
Conclusions
1. Our case demonstrates that in some instances, the produced testosterone by the tumor can have a selective influence on peripheral tissues causing only menstrual irregularity without virilization. Since these tumors have malignant potential, differential diagnosis of ovarian mass with high levels of testosterone is essential even without signs of virilization. 2. Elimination of the interferences by extraction with diethyl ether demonstrated that the cause of pitfall in total testosterone level was hydro soluble fragments of the steroid hormone pathway which react with testosterone antibodies in the direct assay.

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Remission of ovarian hyperandrogenism in two post-menopausal women treated with GnRH analogue

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Background and aim
Ovarian hyperandrogenism is a known cause of post-menopausal hirsutism and virilisation, more frequently of a benign nature (e.g. ovarian hyperthecosis, Leydig cell hyperplasia). Bilateral salpingo-oophorectomy delivers both definitive diagnostic and therapeutic results. However, after excluding the presence of a suspicious ovarian mass, the use of GnRH analogues (GnRH-a) offers a valuable therapeutic alternative with cases reporting a sustained response in time, besides suggesting an ovarian origin of the hyperandrogenism by their suppressive action on gonadotropins.
Cases presentation
Two post-menopausal women (aged 73 and 74 years) presenting with progressive hirsutism and alopecia were referred to our unit for further evaluation. They both showed high testosterone (T) levels (1.71 and 0.80 ng/ml, respectively), not adequately suppressed after low-dose dexamethasone suppression test (48-h 2 mg/d) and dosable oestradiol (E2) levels. All other steroidal hormones were in the normal range. The second patient underwent videodermatoscopy, showing an increase of hair diameter variability $>$20%, some empty follicles, peripilar depressions and some small short regrowing hair. No ovarian or adrenal findings suspicious for malignancy were found at the abdominal CT scan and pelvic US. The pituitary MRI scan was within the normal range. We started both patients on a 3-month treatment with GnRH-a (triptorelin 3.75 mg im injection every 28 days) to confirm the presumed ovarian origin of T overproduction and to achieve both clinical and biochemical regression of their hyperandrogenic condition.
Results
We re-evaluated both patients one month after the first GnRH-a injection, three months after the last injection and then every 4-6 months, up to 2.5 years after the treatment initiation for the first patient. Both patients showed suppression of gonadotropins and E2 levels and reduction in T levels to within the normal range

one month after the first injection (<0.1 and 0.46 ng/ml, respectively). Gonadotropin levels then progressively rose up to a post-menopausal range after finishing the treatment, while E2 levels remained suppressed and T levels remained within a normal range (0.19 and 0.54 ng/ml, respectively). Both patients reported clinical improvement for both hirsutism and alopecia. Videodermatoscopy re-evaluation confirmed a marked trichoscopical improvement.
Conclusions
GnRH-a is a valid choice for the treatment of post-menopausal hyperandrogenism of presumed benign ovarian origin, as an alternative to surgery. It has shown a sustained clinical and biochemical response up to 6 months in both patients and up to 2.5 years for one patient.

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Benificial Effects of Antioxidant Combination in Dimining Oxidative Stress Status and Improves Semen Parameters in Infertile Men: One Blind Placebo Controlled Trial

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Male infertility every year is becoming one of the main problems of the health system, which requires serious steps in coping this health and socioeconomic burden. Oxidative stress is emphasized as the main factor of idiopathic etiology resulting with the inability to conceive because of poor semen quality. Antioxidants have shown their beneficial effects in various studies conducted, resulting both in improving semen quality and higher chance of natural conception. Thus, the aim of this study is to verify the impact and effectiveness of the antioxidant formula both in oxidative stress status and semen parameters. A total of 211 infertile men were enrolled in the study after passing the inclusive criteria, 50 of them were used only for comparison while 161 were divided in two groups: interventional ($n=80$) and the placebo group ($n=81$). Standard semen analysis along with biochemical analysis of malondialdehyde (MDA), caspase-3 (cas-3) and total antioxidant capacity (TAC) levels were analyzed in two points: T_0 (before the antioxidant/placebo therapy) and T_6 (six months after antioxidant/placebo therapy). Mean ± SD and Wilcoxon signed ranks was used to asses changes in two points. After six months the interventional showed significant improvements in terms of sperm concentration ($P=0{,}00006$), motility ($P<0{,}001$) and morphology ($P<0{,}001$), while changes in the placebo group where not statistically significant ($P=0{,}713$, $P=0{,}428$ and $P=0{,}606$, respectively). In the group treated with antioxidants we had a reduction in MDA, Cas-3 levels (6,01 ± 0,83 to 3,25 ± 0,68 and 3,82 ± 0,53; $P<0{,}001$ respectively) and increase in TAC levels (45,53 ± 9,15 to 74,88 ± 12,63; $P<0{,}001$). While in the placebo group the mean MDA, Cas-3 and TAC levels had no statistically significant changes (6,49 ± 1,40 to 6,51 ± 1,45; $P=0{,}65$), (4,11 ± 0,68 to 4,12 ± 0,77; $P=0{,}89$) and (45,41 ± 7,78 to 44,67 ± 8,44; $P=0{,}37$), respectively. Looking at the cost-benefit aspect and rationale behind antioxidant therapy in infertile men, we strongly suggest their use before any other procedure.

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Visfatin expression and regulation by E2, P4, hCG and insulin in human placental cells

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Introduction
Visfatin belongs to adipokines, i.e. hormones produced mainly by adipose tissue; its expression and role have been described in many organs, where it regulates energy metabolism, insulin resistance and inflammatory reactions. Moreover, the level of visfatin changes during pregnancy and in obese women and those with obesity related pregnancy pathologies: preeclampsia (PE), gestational diabetes (GDM) or intrauterine growth restriction (IUGR) its level increases. There is no data about the role of adipokine in placenta so the aim of this study was to: 1) determine the expression and immunolocalization of visfatin in the trophoblast cell lines JEG-3 and BeWo, as well as in the maternal and fetal parts of placentas from normal and PE, GDM and IUGR complicated pregnancies; 2) examine the effect of: estradiol (E_2), progesterone (P_4), human chorionic gonadotropin (hCG) and insulin (INS) on visfatin level in JEG-3.
Materials and Methods
To study the mRNA (real time PCR), protein (Western blot) expression and immunolocalization (immuno -cytochemistry, -histochemistry) of visfatin, JEG-3/BeWo were cultured in time-dependent manner, while fragments of terminal placentas were collected after delivery. Furthermore, the effect of: E_2 (1, 10, 100 nM), P_4 (1, 10, 100 nM), hCG (0.1, 1, 10 ng/ml), INS (10, 50, 100 ng/ml) on visfatin protein expression (Western blot) and concentration (ELISA) was examined. Next, the involvement of signaling pathways of extracellular signal-regulated kinase (ERK 1/2), transcription factor NF kappa B (NF-κB) and receptors (PR, GPR30, ER, LHCGR, INSR) in visfatin regulation was analyzed. Statistical analysis was performed in Graph Pad Prism 7, using one-way ANOVA and Tukey's test ($n=5$, $P<0.05$).
Results
We demonstrated the mRNA and protein expression of visfatin in JEG-3/BeWo cells and in normal/pathological placentas. Our studies showed the immunolocalization of visfatin in cytoplasm of both cell lines, syncytiotrophoblasts of placenta fetal part and capillary epithelium of maternal part while in the pathologies additionally in decidual cells. Moreover, we explored a stimulatory effect of all tested hormones on visfatin level in JEG-3 with the involvement of specific signaling pathways.
Conclusion
Differences in the localization of visfatin in the maternal part of normal and pathological placentas, suggested that adipokine may be a potential marker for pregnancy disorders diagnosis. In addition, variable level of visfatin during individual trimesters may be the result of pregnancy hormones, which stimulate its level in the human placenta cells.
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Sexual dimorphism in the LH responses to kisspeptin and senktide administration in prepubertal mice

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Introduction
The hypothalamic-pituitary-gonadal (HPG) axis is regulated by pulsatile GnRH secretion and its action on the anterior pituitary, leading to the synthesis and secretion of LH and FSH. KNDy neurons, expressing kisspeptin, neurokinin B and dynorphin A, are the GnRH/lH pulse generator and are key regulators of puberty and fertility. The HPG axis is active during prenatal and early postnatal life in humans and rodents, but then remains quiescent until puberty in both species. The response of gonadotropes to exogenous upstream GnRH signals such as kisspeptin and neurokinin during prepubertal development in mice is unknown.
Aim
To conduct a systematic assessment of LH responsiveness to exogenous kisspeptin and to the neurokinin-3 receptor agonist senktide at regular intervals postnatally and across pubertal maturation in mice.
Materials and Methods
Male and female J129Sv mice were treated with intraperitoneal injections of kisspeptin-10 (0.0023 nmol/g), senktide (0.023 nmol/g) or vehicle every 3 days from postnatal day (PND) 10 until completion of puberty. Serum LH was measured by an ultra-sensitive ELISA at baseline and 15 minutes after injection.
Results
Prepubertal mice responded in an age-dependent and sexually dimorphic manner to kisspeptin and senktide. LH levels increased following kisspeptin stimulation in both sexes, but responses were higher in females than in males from PND10 to PND16. The highest response was observed at PND10, with a pattern of decreasing response with advancing age. Senktide induced a robust increase in serum LH in females from PND10 to PND16, with a decrease in response with age, similar to that observed after kisspeptin treatment. In contrast, in males there was no increase in serum LH in response to senktide at any age. No difference in

the onset of puberty or body weight was observed across treatment groups.
Conclusions
The assessment of serum LH levels following IP administration of kisspeptin and senktide in prepubertal male and female mice demonstrated distinct age and sexually dimorphic patterns of LH responses to GnRH upstream signals, with greater responses at early postnatal ages and in females than in males. These findings provide new evidence for sexual dimorphism of the HPG axis in mice early in postnatal life, prior to the onset of puberty, and raise the possibility of additional restraining factors on HPG axis activity in early life.

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Hyperprolactinemia in Turner syndrome

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Introduction
Hyperprolactinemia is a relatively frequent finding. A wide range of conditions can be responsible of this biochemical abnormality. Herein we report a rather rare etiology of hyperprolactinemia which is Turner syndrome (TS).
Methods
Aiming to determine the frequency of hyperprolactinemia in patients with TS, we enrolled a retrospective descriptive study in the department of Endocrinology at the Hedi Chaker Hospital. We included patients who have the cytogenetic confirmation of Turner syndrome and who consulted our department between 1990 and 2021. As for hyperprolactinemia, it is defined as a prolactin level above 25 ng/ml.
Results
The total number of patients in our study was 45. Their mean age of diagnosis was 16 years. Most of them were diagnosed after the age of 10 years (88.9 %). Karyotype analysis revealed the presence of X monosomy in 49 % of cases, mosaicism without structural alterations of X in 31 % and mosaicism with structural variants of the X chromosome in 20 % of cases. Dosage of prolactin was performed in 29 patients with primary amenorrhea. The median prolactin level was 11.7 ng/ml [Q1, Q3: 8.8-16.6 ng/ml]. Four patients had hyperprolactinemia which corresponds to a frequency of 13.8 %. The mean age of these patients was 17.5 years, with extremities ranging from 15 to 21 years. Cytogenetic findings were variable among these patients as one had 45, X, the second had 45, X/46, XX, the third had an Y chromosome and the karyotype of the fourth girl was 46, XX/46, X i(Xq). This latter patient had a positive SRY. As for the mean prolactin level, it was 49.05 ng/ml. The maximum was 60.8 ng/ml. Regarding the etiology of this biochemical abnormality, we excluded hepatic dysfunction, renal insufficiency and hypothyroidism. Drug-induced hyperprolactinemia was also dismissed. A pituitary MRI was performed in two cases and it was normal. The evolution of hyperprolactinemia was marked by its spontaneous regression in two cases: after one year in the first case and after four years in the second. Conversely, the two other patients had persistent hyperprolactinemia.
Conclusion
Hyperprolactinemia is not an exceptional finding in TS. However, gaps remain in our understanding of the pathophysiological mechanisms underlying this abnormality. Therefore, more research is warranted.

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A rare co-occurence of Turner syndrome and acromegaly complicated by the presence of a solid pseudopapillary neoplasm of pancreas-a case report

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Background
Turner syndrome (TS) is the most common chromosome deficiency in women, with an incidence of 1 in 2 000 female newborns. Acromegaly is a rare disease, which occurs with a frequency of 1:140 000–250 000 of the population. To our knowledge only several cases of TS and acromegaly coexistance have been reported up to date.
Case presentation
A 43-year-old woman with TS was referred to our Department with an accidentally discovered pituitary macroadenoma (3.5×3.4×2.6 cm). The patient presented a typical picture of acromegaly and has been chronically taking hormone replacement therapy due to hypogonadism in the course of TS. In our Department hormonal tests revealed hyperprolactinemia (PRL = 46.8ng/ml) and active acromegaly (IGF-1 = 962 ng/ml; GH = 74.4 μg/l). In the dermatological and pathomorphological consultations multiple skin neurofibromas were described. A well-defined unenhanced lesion 70x58x77 mm in size, with thick wall, fluid level and a heterogeneous content was described in the abdominal MRI. The endoscopic ultrasound-guided fine needle aspiration did not succeed. Somatostatin receptor scintigraphy revealed an abnormal radiolabel uptake of the pituitary tumor and did not show any other lesions with pathological radiotracer accumulation. While awaiting for pituitary surgery the patient was administered lanreotide autogel 120 mg every 4 weeks s.c. for acromegaly, bromocriptine 2,5 mg/day due to the coexistance of hyperprolactinemia. After 5 months of preoperative medical treatment transsphenoidal pituitary adenoma resection was performed. A pathological report revealed a mixed somatotroph and lactotroph PitNET with GH, α-subunit and PRL positive immunostaining and Ki-67 labeling index 1%. Due to the persistent active acromegaly (IGF-1 = 442 ng/ml; GH = 3 μg/l) after the operation the treatment with lanreotide autogel was restarted which resulted in complete biochemical acromegaly control after 6 months. After surgical, gastroenterological consultations, the patient was qualified for pancreatic tumor resection and the pathology report revealed solid pseudopappilary neoplasm of the pancreas (SPNP): Vim (+++), cyclin D1 (+), PGR (++/+++), CD10 (+++).
Conclusions
To date, the coexistence of TS and acromegaly is considered a rare coincidence. Despite the presence of multiple skin neurofibromas in our patient, the diagnosis of neurofibromatosis type 1 was excluded. SPNP which is a very rare tumor of the pancreas is usually described in females under the age of 30 years, however the effect of estrogens and progesterone on SPNP remains still uncertain. In order to expand the knowledge it is necessary to collect similar cases to assess the effect of GH excess in TS.

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***In vitro* evaluation of the impact of two differently glycosylated recombinant FSH on signal transduction**

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Follicle stimulating hormone (FSH) is produced by the anterior pituitary gland and it is a key hormone in the reproductive system. FSH is a heterodimeric glycoprotein composed with two extensively glycosylated protein sobunits (α and β) N-glycosylated in two positions (Asn^{52} and Asn^{78} in the FSHα subunit and Asn^{7} and Asn^{24} in the FSHβ subunit) giving rise to numerous isoforms of FSH. Glycosylation has been shown to impact on the *in vivo* activity of FSH by influencing its clearance and its ability to bind and activate receptors. Different FSH glycoforms are used for assisted reproduction. The aim of this study *in vitro* is to compare the intracellular signaling pattern mediated by two differently glycosylated, recombinant FSH. Gonal-f® (Merck KGaA) is produced using a modified chinese hamster ovary (CHO) cell line while Rekovelle® (Ferring Pharmaceuticals) is produced by the human fetal retinal PER.C6® cell line. Transfected HEK293 cells overexpressing the FSH receptor (FSHR) were treated by increasing FSH doses (0.0-1.0 μM range). The intracellular cAMP and Ca^{2+} increase, IP1 production, FSHR homomers formation and the evaluation of transcriptional activity of genes dependent on cAMP and pERK1/2 activation, using both CRE- and NFAT-luciferase reporter assay, were evaluated by energy transfer-based methods. Results were compared by two-way ANOVA and Bonferroni post-test ($P<0.05$). The two differently glycosylated rFSH impact differently on FSHR homomer formation ($n=4$). No statistically significant difference was evaluated regarding the intracellular accumulation of cAMP ($n=6$). However, Gonal-F® is more effective than Rekovelle®. Gonal-f® was less potent but more effective than Rekovelle® in activating the CRE-controlled reporter gene ($n=5$). Furthermore, Rekovelle® induced a biphasic response, at low concentrations it is

more potent than Gonal-f® while at high concentrations it seems to inhibit the activation of the reporter gene controlled by CRE. In order to understand the contribution of 'non-classical' FSH-dependent pathways, not necessarily dependent on cAMP, on cell functions the CRE-controlled reporter gene activation was evaluated in the presence or absence of Dynasore or specific PKA, PLC, AKT, MEK-ERK1/2 inhibitors ($n=6$). The two differently glycosylated rFSH induce a different signal pattern given by the activation of CRE-controlled reporter gene in the presence of inhibitors except in the presence of AKT inhibitor. Rekovelle® is more potent to induce intracellular Ca^{2+} release ($n=6$) than Gonal-F® but no different IP1 production and NFAT-controlled reporter gene activation were detected ($n=4$). Recombinant FSH used in clinical practice may impact differently intracellular signaling cascades *in vitro*.

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P469

Gestational thyrotoxicosis due to molar pregnancy complicated by pre-eclampsia

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Introduction
Gestational trophoblastic disease (GTD) is a group of disorders arising from abnormal proliferation of placental trophoblasts. Hydatiform mole (molar pregnancy) is a premalignant condition which is further devided in to partial and complete mole. Incidence of molar pregnancy is estimated to be 1 in 1000 pregnancies. Hyperthyroidism is one of the rare complications of molar pregnancy which, if not detected and treated, can lead to adverse consequences. We describe the case of a 42-year old lady, who presented to the hospital at a gestational age of 10 weeks.
Case History
Her symptoms at presentation included vaginal spotting and palpitations of 5 days onset. The background included hypertension following her last pregnancy, on treatment with labetalol 200 mg, pre-eclampsia, two previous spontaneous miscarriages, four spontaneous vaginal deliveries. At the time of assessment, pulse rate was 95/min, and the blood pressure 185/118 mmHg up to 199/123mmHg. The electrocardiogram showed sinus rythm. An ultrasound scan showed large multi-cystic/haemorragic lesion measuring 82 x 110 x 66mm within the endometrium in keeping with a complete molar pregnancy. The blood tests showed: thyroid stimulating hormone (TSH) of <0.01 munit/l (Range: 0.3-4.2nunit/l), Free thyroxine of >100pmol/l (Range: 12-22pmol/l), Free T3 of 28.6pmol/l (Range: 3.1-6.8pmol/l), b-chorionic gonadotrophin (b-HCG) levels 553,445units/l, alanine aminotransferase 47units/l, aspartate aminotransferase 41units/l. The urine was positive (++) for protein. Burch-Wartofsky score was 20, making thyroid strom less likely. Given the clinical picture of mild thyrotoxicosis she was started on carbimazole 60 mg daily, and continued on Labetalol 200 mg three times per day. She underwent surgical removal of molar pregnancy with uneventful post-operative course. One week later she was weaned off carbimazole. Histology confirmed the diagnosis of molar pregnancy, and her thyroid function test (TSH: <0.01munit/l, FT4: 11.7pmol/l) with bHCG levels (573 units/l) normalised two weeks later. Following discharge, the results of the thyroid receptor antibodies (<0.4 units/l) were made available, and confirmed the diagnosis.
Discussion
The clinical and biochemical picture of this patient were compatible with GTD, on the background of molar pregnancy. The sinus tachycardia was likely related with the early onset of pre-eclampsia. Careful clinical assessment is required to ensure the clinical signs are correctly interpreted prior to the surgery, as thyroid storm can easily be triggered in the context of an incorrect diagnosis. Surgical removal of mole is the definitive treatment in these cases. HCG and thyroid function test should be monitored afterwards to ensure gestational trophoblastic neoplasia doesn't develop.

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P470

Unveiling follicular fluid oxidative stress biomarkers at polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrine disorder of women at reproductive-age and accounts for 80% of the causes of anovulatory infertility. Despite the widely characterized reproductive, endocrine, and metabolic abnormalities, the mechanisms underlying PCOS remain unclear. Thus, it is essential to identify novel biomarkers that will allow to disclosure novel pathways involved PCOS pathophysiology, which could then be used to improve PCOS management and treatment. Although oxidative stress has been suggested to play a central role in PCOS associated reproductive dysfunction, the potential use of follicular fluid (FF) oxidative stress-related molecular profiling as reproductive function biomarker in women with PCOS, has not been widely explored. Herein, we investigated and compared the levels of lipid peroxidation (LPO) and total antioxidant capacity (TAC) FF of women with and without PCOS undergoing *in vitro* fertilization (IVF), in addition, the association between those oxidative stress markers and IVF outcomes was examined. A total of 84 women were enrolled in this study, 30 women with PCOS and 54 women ovulatory controls. FF was obtained from mature follicles at the time of oocyte retrieval. Oxidative stress was examined by measuring TAC levels by ferric reducing antioxidant power (FRAP) and by assessing LPO through quantification of malondialdehyde levels at the FF. Our results showed that TAC levels were lower in the FF of women with PCOS when compared to the non-PCOS group (1.704 ± 0.275 vs 2.903 ± 0.43; $P<0.0001$). There were no significant differences in LPO levels, although these levels tended to be higher in PCOS group compared with the non-PCOS group (19.23 ± 1.68 vs 16.66 ± 1.34). No correlation was found between LPO or TAC levels and the number of oocytes retrieved and fertilized, cleavage and fertilization rate. Unravelling FF profile of women with PCOS may help the recognition of potential biomarkers that disturb normal female function leading to infertility problems. Overall, our preliminary findings suggest that oxidative stress is involved in the pathophysiology of PCOS and, therefore oxidative stress parameters may be crucial to understand the mechanisms underlying the manifestations of this syndrome.

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P471

Establishing LOQ for estradiol, LH, FSH and testosterone on Roche Cobas e801

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Introduction
The limit of quantification (LOQ) is defined as the lowest analyte concentration that can be reproducibly measured with defined imprecision expressed as CV (coefficient of variation). Low concentrations of hormones estradiol, LH, FSH and testosterone are essential in diagnosis and monitoring of various endocrine disorders. Automated immunoassays have well known advantages, but still limited in achieving necessary analytical sensitivity. The major concern is to produce low values with low imprecision. Our aim was to determine the lowest concentration of the listed hormones with CV $<20\%$.
Aterials and Method
According to LOD (limit of detection) and LOQ declared by the manufacturer we selected similar estradiol, LH, FSH and testosterone concentrations. Serum pools were prepared from patients residual samples. Final pool concentrations were: (i) estradiol 88,9 pmol/l, 50,7 pmol/l and 27,4 pmol/l; (ii) LH and FSH 0,3 IU/l; (iii) testosterone 0,5 nmol/l and 0,17 nmol/l. Pools were analyzed over five days in triplicates on Roche Cobas e801 and CV was calculated. Inter-assay variation (bias) was eliminated by analyzing all specimens in a single batch using a single instrument, one analyst, one set of calibrators with the same lot of reagents.
Results
The determined CV for estradiol at 88,9 pmol/l, 50,7 pmol/l and 27,4 pmol/l was 6,0%, 9,3% and 19%, respectively. The remaining pools obtained CVs as follows: 4% for LH at 0,3 IU/l; 2,3% for FSH at 0,3 IU/l; 4,9% and 7,8% for testosterone at

0,5 nmol/l and 0,17 nmol/l.
Conclusion
All selected estradiol, LH, FSH and testosterone concentrations met the defined criteria of CV <20%. Therefore, they represent the reliably measured low concentrations on analytical system Roche Cobas e801 and could be defined as LOQ.
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P472

Normosmic idiopathic hypogonadotropic hypogonadism: A case report
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Background
Idiopathic hypogonadotropic hypogonadism (IHH) is manifested as absent or incomplete puberty and biochemically low levels of sex hormones, with low or inappropriately normal gonadotropin hormones. In the absence of structural or functional lesions of the hypothalamic or pituitary gland, the hypogonadism is referred as idiopathic hypogonadotropic hypogonadism (IHH). IHH is a genetically heterogeneous disorder which can be caused by pathogenic variants affecting proteins involved in the pulsatile gonadotropin-releasing hormone release, action, or both.
Case Presentation
A 16-year-old male who presented to the endocrinology clinic with complaints of micropenis and absent secondary sex characteristics. Work up showed an unremarkable cranial MRI, low testosterone, LH, normal FSH, with normal Karyotyping.
Conclusions
Idiopathic hypogonadotropic hypogonadism (IHH) is a rare genetic disease with a complex and still have more to discover about its pathogenesis. The requirements for the diagnosis include low testosterone, low or normal serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations, and a normal appearance of the hypothalamus and pituitary region on magnetic resonance imaging (MRI). A prompt recognition of a clinical hypogonadotrophic hypogonadism is pivotal especially in a peripubertal age to initiate early sex hormone replacement as the failure of secondary sex characteristics could have a derogatory impact on individual's personal and social life.
Keywords
Hypogonadism, Idiopathic hypogonadotropic hypogonadism (IHH)
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P473

Change in lipid profile and glucose levels after 12 months of testosterone therapy in transgender men
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Introduction
Approximately 0.5% of the world population experiences gender dysphoria, a discrepancy between one's biological sex and gender identity. Transgender men (TM), individuals who were assigned female at birth but who identify as men, can benefit from therapy with testosterone (T) to address gender dysphoria. Although unfavourable changes in lipid profiles have been previously reported, most studies did not show an adverse impact of testosterone treatment on fasting glucose levels.
Methodology
We performed a retrospective analysis to compare lipid profile - total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides (TG) levels-, fasting plasma glucose (FPG) levels and weight, from baseline to 12 months after the initiation T therapy. We included a cohort of 60 TM who attended our clinic from January to December 2021. After assuring normal distribution of the variables using Kolmogórov-Smirnov test, we performed a Paired samples t-test to compare pre- and post-treatment parameters. Results were presented as total number (percentage) for qualitative variables and as mean ± standard deviation for quantitative variables. Statistical analysis was conducted using SPSS software v.23.
Results
The mean age of our cohort was 20.6 ± 5.3 years and 16 of them (26.7%) were smokers. Regarding T therapy, 15 of TM (25%) were using transdermal testosterone, 32 (53.3%) testosterone undecanoate and 13 (21.7%) testosterone cypionate. Lipid profile, FPG and weight, baseline and 12 months after the initiation of testosterone therapy were compared (Table 1). A significant increase in LDL levels (mean difference +6.050, $P = 0.008$) and a significant decrease in HDL levels (mean difference -8.050, $P < 0.001$) were observed. These changes did not correlate with testosterone levels or treatment modality.
Conclusion
As observed in other publications, this study shows a significant impairment in LDL and HDL levels 12 months after the initiation of testosterone treatment. Unlike, no worsening in FPG levels or weight gain were observed. We should take these results into consideration to address cardiovascular risk and promote positive changes in lifestyle to TM who start testosterone therapy.

Measurements	Baseline	After 12 months of T	*P* values
TC(mg/dl)	169.7 ± 25.0	167.4 ± 28.8	$P = 0.342$
LDL(mg/dl)	96.9 ± 22.9	102.9 ± 27.0	$\mathbf{P = 0.008}$
HDL(mg/dl)	56.3 ± 11.6	48.3 ± 9.3	$\mathbf{P < 0.001}$
TG(mg/dl)	73.7 ± 30.5	78.5 ± 31.2	$P = 0.261$
FPG (mg/dl)	87.2 ±8.0	84.4 ± 10.5	$P = 0.060$
Weight (Kg)	66.2 ± 14.6	66.8 ± 12.6	$P = 0.525$

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P474

Significant hyponatremia as a manifestation of severe pre eclampsia
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A 32-year-old primigravida woman, low risk pregnancy, BMI 20, presented at 29 weeks of gestation with headache and mildly raised blood pressure and normal laboratory tests. The patient had no signifcant medical history and the pregnancy to date had been uneventful. Physical examination showed blood pressure (BP) of 145/93 mm Hg. (Baseline, 100/70 mm Hg). Laboratory tests showed a baseline sodium of 134 mmol/l, with the rest of the biochemistry normal. She had been commenced on Labetalol. At 29+4 weeks, the patient was admitted with headache, feeling unwell, leg and hand oedema and raised blood pressure. Physical examination showed BP of 168/105mm Hg with significant pedal oedema and proteinuria +4. Other physical findings were unchanged. Laboratory investigations showed serum sodium level of 122 mmol/l), with normal kidney and liver function test results. A urine osmolality was elevated at 433 mmol/kg while her urine sodium measured at 22 mmol/l and her urine potassium at 33 mmol/l. A short synacthen test was normal including normal thyroid biochemistry. The patient was admitted for observation including blood pressure monitoring. Liver function test results and serum uric acid level were normal. A growth scan of the foetus showed normal growth. Subsequent BP readings were under control while her urine protein creatinine ratio was 100 mg/mmol. During her hospital stay, her serum sodium level continued to decline. Although she was put on fluid restriction, her hyponatremia continued to worsen, with development of generalised oedema and imaging picking up sub pulmonary pleural effusion and mild pericardial effusion. Volume overload signs included engorged neck veins, presacral oedema were evident. Laboratory signs of severe preeclampsia as elevated liver enzymes (ALT 248), thrombocytopenia (platelets at 77) was also seen. In addition, her urine protein creatinine ratio had further increased to 416 mg/mmol. Essentially, she had developed severe hyponatremia in the setting of preeclampsia. Decision for delivery was made at 30 weeks by elective CS and planned admission to intensive care unit after multidisciplinary team discussion including obstetrician, Endocrinologist, neonatologist, cardiologist and anaesthetist. She was delivered by caesarean section, which was uneventful. Magnesium sulphate was given before delivery for neuroprotection and continued 24 hrs post-partum to reduce the risk of seizures. Serum sodium levels improved after 48 hrs post-delivery and returned to normal values on day 5 post-partum as well as the oedema. This presentation highlights the importance of hyponatremia as a prognostic factor guiding management of severe pre-eclampsia.
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P475

Not what it seems: an exuberant case of hirsutism in polycystic ovary syndrome
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Introduction
Hirsutism is the presence of terminal hair growth in females with a male distribution pattern. It affects 5-15% of women, being an important sign of androgen excess. The main causes of hirsutism are polycystic ovary syndrome (PCOS) and idiopathic hyperandrogenism. Other significant but less frequent causes of hirsutism include nonclassic congenital adrenal hyperplasia (NCAH), androgen-secreting tumors, and Cushing's syndrome.
Case report
A 24 year old obese female patient was referred to the Endocrine Department due to marked hirsutism, which began at the age of 15 and worsened from 18 years onwards. She had no other complaints. Menarche occurred at 13 years old. Even though her menstrual cycles were initially regular, she was in amenorrhea for the past 5 years. She had no history of pregnancy and had never taken oral contraceptives. She was medicated with sertraline for depression and topiramate for chronic headaches. There was no known family history of hirsutism. On physical examination, the patient had a BMI of 36.8 kg/m2, acanthosis nigricans, a Ferriman-Gallwey score of 31 and a marked androgenic pattern alopecia. Blood pressure was normal and there were no purple striae, proximal myopathy or other signs of virilization such as acne or voice changes. The blood tests showed normal thyroid function, prolactin and gonadotropin levels, an estradiol of 46.3 pg/ml (NR 12-398), total testosterone 61.9 ng/dl (NR 5-48), free testosterone 3.40 ng/dl (NR <4.2), SDHEA 347 µg/dl (NR 98-340), delta-4-androstenedione 5.13 ng/ml (NR 0.3-3.7) and a basal 17OH-P 1.30 ng/ml (NR <2), which excluded NCAH. The dexamethasone 1 mg suppression test also excluded Cushing's syndrome, with a cortisol of 0.6 µg/dl. A CT scan of the abdomen showed no changes of the adrenal glands. Pelvic ultrasound showed increased volume of both adnexa (14 and 13cc), globous, with sonolucent formations of both central and peripheral location, features suggestive of micropolycystic ovaries. The diagnosis of PCOS was assumed, and the patient was medicated with daily drospirenone, ethinyl estradiol and ciproterone acetate 10 mg (for 15 days of the menstrual cycle), with no perceived improvement. Mechanical terminal hair removal was encouraged.
Conclusions
Androgen levels correlate poorly with hirsutism severity in PCOS, given that clinical manifestations are dependent on the individual's pilosebaceus unit response to androgens. Therefore, individuals can present with very exuberant hirsutism, suggesting more serious underlying disease, despite modest androgen levels, as in the case of our patient.

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P476

Galanin-Like Peptide and its' Correlation With Androgen Levels in Patients with Polycystic Ovary Syndrome

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Introduction
We aimed to investigate serum galanin-like peptide levels and its'correlation with hormonal and metabolic parameters in patients with polycystic ovary syndrome (PCOS)
Material and Methods
The study included 48 women (age range, 18-44 years) with a diagnosis of PCOS and control group that included 40 healthy females (age range, 18-46 years). Body mass index (BMI), waist circumference, Ferriman-Gallwey score, was evaluated and plasma glucose, lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides), estradiol, progesterone, total testosterone, prolactine, insulin, DHEA-S, FSH, LH, free T3, free T4, TSH, anti-TPO, 25(OH)D, fibrinogen, d-dimer, CRP and GALP levels were measured in all study subjects.
Results
Waist circumference ($P=$ 0,044) and Ferriman-Gallwey score ($P=$ 0,002) were significantly higher in patients with PCOS compared to control group. Among the metabolic and hormonal parameters studies, only total testosterone was significantly higher in patients with PCOS ($P=$ 0,002). Also, serum 25(OH)D level was significantly lower in PCOS group ($P=$ 0,001). CRP, fibrinogen and D-dimer levels were all similar between the two groups. Serum GALP level was significantly higher in PCOS patients ($P=$0,001). GALP was negatively correlated with 25(OH)D ($r=$-0.401, $P=$ 0.002) and positively correlated with total testosterone values ($r=$ 0.265, $P=$ 0.024)) Multiple regression analysis revealed that both total testosterone and 25(OH)D significantly contributed to GALP levels.
Conclusions
Our study is the first study in the literature that evaluated serum GALP levels in patients with PCOS. Increased GALP levels in PCOS and its' association with total testosterone levels, might show that GALP may act as an intermediary in increased GnRH mediated LH release that is one of the underlying pathogenetic mechanism of PCOS.

Key Words
Galanin-like peptide, vitamin D, polycystic ovary syndrome
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P477

Hidden Cause of Decreased Fertility Rate During Grave's Disease

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Introduction
Thyroid autoimmune disorders interfere with the physiology of reproduction, cause premature ovarian aging, and mimic the early stage of menopause. Recently, no specific research was made to measure Grave's disease and infertility rates in young patients.
Case Report
Due to an inability to conceive for two years, a 24-year-old Caucasian female was referred to the clinic with typical symptoms and complaints of Grave's disease. She has a family history of Grave's disease and Diabetes mellitus. Ultrasound confirmed the presence of a highly vascularized non-homogeneous hyperplastic thyroid gland. A thyroid scan with Tc99m revealed generalized increased uptake. Laboratory investigations showed a decrease in TSH-<0.005mIU/ml (n.0.4mIU/ml - 4.0mIU/ml), elevated FT4-31.8 pmol/l (n.8.0pmol/l-22.0pmol/l), FT3- 9.69pmol/l (n3.4 pmol/l-6.76pmol/l) and positive Anti-TG -190.05 AU/ml (n>150), Anti-TPO - 75.7 IU/ml (n>75) Anti-TSHR-27.3 IU/l (n>1,5). Prolactin and gonadal hormones were within normal limits AMH - 1.8 ng/ml(n1.52ng/ml-9.95ng/ml), Fsh-6mIU/ml(n3.9mIU/ml-12.4mIU/ml). The patient was started on Methimazole and Beta-blocker. While decreasing the Methimazole dosage for further discontinuation, disease recurrence developed, and a total thyroidectomy was performed. Post-operatively, the patient was maintained on Levothyroxine. After 6 months of follow-up due to irregular Levothyroxine intake, the patient reached a hypothyroid status, during which, the patient had 2 consecutive spontaneous pregnancies, from which, one ended with spontaneous miscarriage in the early weeks of pregnancy and another, ectopic pregnancy treated with right salpingectomy. HSG confirmed weak left fallopian tube patency. After several months of keeping TSH below 2.5 mIU/ml, IVF treatment was scheduled. The results of the infertility workup showed a decrease in ovarian reserve AMH - 0.163ng/ml (n1.52ng/ml-9.95ng/ml), Fsh-16.23 mIU/ml(n3.9mIU/ml-12.4mIU/ml), due to it, modified natural cycle IVF was performed. She received 2 oocytes and 2 embryos. One high-grade blastocyst was transferred in a fresh cycle that ended with pregnancy and delivery. The child was born without a genetic disorder but with natal teeth.
Conclusion
This is a rare case of infertility with diminished ovarian reserve due to Grave's disease. A pregnancy was reached by proper correction of thyroid hormonal parameters and modified natural cycle IVF. It indicates a possible need for close monitoring of the functional ovarian reserve in patients planning pregnancy even in the young age group.

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P713

A case of prolactin increase with cyproterone acetate: sublingual use of estradiol in transgender woman

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Introduction
Transgender women and gender diverse individuals with functioning testicles who are eligible for estrogen-based hormone therapy need to use antiandrogens in addition to estrogen to achieve adequate desired physical changes and suppress testosterone to cisgender women levels. Sublingually administered estradiol can achieve higher serum estradiol levels than traditionally administered oral estradiol, but may require multidaily dosing (1). We present a case of transgender woman who uses estrogen sublingually and cyproterone acetate as antiandrogen.

Case
Twenty-four years old transgender woman has been using estradiol in dose of 1 mg four times a day sublingually for 6 months. She has been started on cyproterone acetate 12.5 mg/day as antiandrogen. She has no chronic disease in her past medical history. During her fourth month follow-up visit, the laboratory values as FSH:1.93 U/l, LH: 5.4 U/l, estradiol 131 pg/ml, testosterone <12 ng/dl, prolactin level was 141.2 mg/l. When the prolactin level was measured in other day, it confirmed the high prolactin levels. She has no galactorrhea. There was no gender affirming surgery in her medical history. She has no complaint of headache or visual problems which could accompany with pituitary adenoma. Cyproterone acetate was stopped and after 6 week of period in which sublingual estradiol was the only gender affirming hormonal therapy, prolactin level turned back to normal levels as 15.7 mg/l. She continued to have sublingual estradiol as gender affirming hormonal therapy. Appropriate testosterone suppression was provided with estrogen only therapy.
Conclusion
Hyperprolactinemia can be seen in transgender women receiving gender affirming hormonal therapy. Cyproterone acetate could be a cause for high prolactin levels. Not only cyproterone acetate but also there are cases in the literature that shows prolactin increase with sprinolactone use as antiandrogen. It has been shown that normalization of prolactin levels occurs when cyproterone acetate is ceased. However, antiandrogens is generally needed to provide suppression of testosterone levels in transgender women. In our case, cyproterone acetate caused increase in serum prolactin levels although it has been given in low doses. We would like to draw attention to the fact that sublingual use of estradiol could provide better serum estradiol levels and testosterone suppression compared to oral use of estradiol.
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P714

Newly diagnosed diabetes in Turner syndrome: what is the role of incretins?

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Introduction
Diabetes mellitus (DM) develops early in Turner syndrome (TS) and appears not related to common risk factors. The precise mechanism of its development is still a matter of debate: a defective insulin response seems to be involved, but the role of incretins is still undefined.
Objective
To evaluate the implication of incretin release in the early stages of DM development in TS.
Materials and Methods
153 Turner patients with normal glucose tolerance (NGT) state at baseline were prospectively evaluated for DM development until 2020 (75 gr OGTT every two years). Samples were collected at 0, 30, 60, 90 and 120 min: glucose and insulin dosage was immediately performed, while incretins were dosed at study end on samples stored at -80°. 10 TS with newly diagnosed DM (120 min glucose ≥ 200 mg/dl) and 10 NGT TS (0 min glucose <100 mg/dl and 120 min glucose <140 mg/dl) were finally evaluated. 19 females comparable for age, BMI and waist circumference were used as controls, 6 with a new diagnosis of type 2 DM and 13 with NGT. An autoimmune cause of DM was excluded by dosing specific autoantibodies. EMD Millipore Corporation© kits were used to measure incretins, through enzyme linked immunosorbent assay (ELISA).
Results
Within controls, insulin to glucose ratio (INS/GLUC) was significantly higher in DM compared to NGT at OGTT 0 ($P=0.003$), 90 ($P=0.052$) and 120 min ($P<0,001$). Differently, within TS, INS/GLUC ratio was comparable between DM and NGT, except a borderline significant decrease at times 60 ($P=0.062$) and 90 min ($P=0.064$) in DM; INS/GLUC total area under the curve was also tendentially decreased ($P=0.081$) in DM vs NGT. GLP-1 levels were similar in TS NGT and DM patients at any time during OGTT, while baseline GLP-1 was significantly higher in DM vs NGT controls (57.5pmol/l$\pm$19.0 vs 34.2 $\pm$ 7.80; $P=0.05$) and higher with a borderline significance at 30 and 60 min ($P=0.072$; $P=0.058$). Regarding GIP, DM controls had higher levels than NGT controls only at 30 min (100.9pmol/l$\pm$35.0 vs 68.8$\pm$30.9, $P=$ 0.046), but there was no such distinction in TS.
Conclusions
In TS, DM has a specific pathogenesis, with insulin secretion deficiency present since the earliest stages. This study suggests that incretins are one of the mechanisms potentially involved in the pathogenetic process, probably through an insufficient release. Further studies on larger cohorts will be needed to provide stronger results and guide clinical practice.
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P715

A systematic review of gonadotropin and GnRH therapy for the induction or completion of puberty in males with hypogonadotropic hypogonadism

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Background and aims
Hypogonadotropic hypogonadism is characterised by inadequate secretion of gonadotropins (luteinising hormone (LH) and follicle-stimulating hormone (FSH)) leading to absent, partial or arrested puberty. In males, classical treatment with testosterone promotes virilisation but does not facilitate testicular growth or spermatogenesis. Conversely, treatment with gonadotropins or gonadotropin-releasing hormone (GnRH) stimulates Sertoli and Leydig cells directly, leading to increased testicular volumes, appropriate serum testosterone concentrations and spermatogenesis. To quantify treatment practices and efficacy, we aimed to systematically review all studies investigating gonadotropin and GnRH therapies for the induction or completion of puberty in males with hypogonadotropic hypogonadism.
Methods
A systematic review of Medline, EMBASE, Global Health, and PsychInfo databases was conducted in December 2022, with RoB 2.0/ROBINS-I/NHLBI scoring for quality appraisal. Protocol registered on PROSPERO (CRD42022381713). Eligibility criteria: studies since 1990 of patients with hypogonadotropic hypogonadism treated with gonadotropins/GnRH for 6+ months assessing pubertal outcomes, including testicular volumes, penile length, LH/FSH, testosterone, inhibin B, anti-Müllerian hormone (AMH), spermatogenesis and fertility.
Results
After screening 3,917 abstracts, 102 studies met inclusion criteria (78 pre-post observational studies, 18 comparative non-randomised studies, 6 randomised controlled trials), including 4,945 patients from 24 countries. Median NIHLBI score for observational studies was 9/12 (interquartile range (IQR) 8-10) and 41.6% of comparative studies had serious risk of bias in at least one domain. The average age of participants was <25 years in 47.1% ($n=48$) of studies. The most frequently described gonadotropin was hCG ($n=96$, 94.2% of studies), followed by FSH ($n=36$, 35.3%) and hMG ($n=36$, 35.3%). 22.5% ($n=23$) of studies described use of GnRH. Median reported duration of treatment/follow-up was 17 months (IQR 10-24 months). 73 studies described change in testicular volume, and 51 of 55 statistical analyses (92.7%) reported a significant increase in size post-treatment. Among other outcomes, 12 studies (11.8%) assessed penile length, 27 (26.4%) LH, 35 (34.3%) FSH, 73 (71.6%) testosterone, 14 (13.7%) inhibin B, 7 (6.9%) AMH, 67 (65.7%) spermatogenesis and 31 (30.4%) fertility. 37 (36.2%) of studies characterised adverse effects, most frequently local reactions, changes to biochemical parameters, acne and gynaecomastia.
Conclusions
There is a growing body of evidence regarding the use of gonadotropins or GnRH for attainment of pubertal outcomes in patients with hypogonadotropic hypogonadism and outcomes are promising. However, there remains substantial heterogeneity in terms of treatment choice, dose, duration, and outcomes assessed, and in particular, randomised studies are needed to increase the quality of evidence for this important patient group.
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P716

Interleukin-22/Interleukin-22 binding protein axis and oral contraceptive use in polycystic ovary syndrome

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Background and Aim
Polycystic ovary syndrome (PCOS) is associated with compositional and functional alterations in gut microbiota. The cytokine interleukin-22 (IL-22) is produced by both innate and adaptive immune cells and closely linked to gut immunity. IL-22 is tightly controlled by its binding protein (IL-22BP), which serves as an antagonist of IL-22 signaling. Preliminary animal studies and limited human data in Asian populations suggest lower circulating levels of IL-22 in PCOS. In this study, we aimed to assess whether IL-22/IL-22BP axis is altered in PCOS at baseline and in response to short-term oral contraception.
Methods
We have evaluated circulating concentrations of IL-22 and IL-22BP in serum samples of 63 PCOS patients and 39 age- and BMI-matched healthy controls who were enrolled for PCOS follow-up studies previously. Blood samples were taken in the early follicular phase of a cycle and stored at -80 ^{0}C. Serum IL-22 and IL-22BP levels were measured by ELISA at baseline in both women with PCOS and controls, and after 3 months of OC use in PCOS group. IL-22/IL-22BP ratio was calculated in order to have a better reflection of IL-22 biological activity.
Results
At baseline, serum IL-22, IL-22BP concentrations and IL22/IL-22BP ratio were similar between women with PCOS and healthy controls. Three months of OC use along with general lifestyle advice resulted in a significant increase in IL-22/IL-22BP ratio in the PCOS group. (62.4 [IQR:14.7-172.7] at baseline vs 73.8 [IQR:15.1-264.3] after OC use respectively $P=0.011$).
Conclusions
Results of the current study show that women with PCOS have similar circulating concentrations of IL-22 and IL-22BP with healthy women and that short term oral contraception is associated with an increase in IL-22/IL-22BP ratio suggesting higher biological activity of the IL-22 system with OC use in PCOS.

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P717

Phenotypic and genotypic variation in pubertal presentation among patients with self-limited delayed puberty and hypogonadotrophic hypogonadism

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Introduction
Delayed puberty (DP), affecting over 2% of adolescents, is defined as pubertal onset at 2-2.5 SDs later than the general population. Two common underlying aetiologies are self-limited DP (SLDP) and congenital hypogonadotrophic hypogonadism (HH). However, these can be difficult to discern between on first presentation of a patient to endocrinology services. This study sought to elucidate phenotypic and genotypic differences between the two diagnoses in order to optimise patient treatment and pubertal progression.
Methods
This was a retrospective study of a UK DP cohort managed from 2015-2022, identified through the NIHR clinical research network. Patients were diagnosed with SLDP if they had attained Tanner stage G4/B4 by age 18 years. Alternatively, they were diagnosed with HH if they had not commenced (complete, cHH) or had arrested puberty (partial, pHH) prior to age 18 years. Phenotypic data pertaining to auxology, Tanner staging, biochemistry, bone age and hormonal treatment were analysed. Genetic scores for likelihood of HH were assigned from 1-5 after whole-exome sequencing and identification of predicted pathogenic variants in genes associated with either SLDP or HH (1=known SLDP variant, 2=likely SLDP variant, 3=no or overlap variant, 4=likely HH variant, 5=known HH variant). Statistical analysis was completed using IBM SPSS and R.
Results
78 patients were included in this study. 52 (66.7%) patients had SLDP and 26 (33.3%) patients had HH, comprising 17 (65.4%) pHH and 9 (34.6%) cHH patients. Probands were predominantly male (90.4%). Male SLDP patients presented with significantly lower height and weight SD than HH patients ($P=0.004$, $P=0.021$). HH patients had lower testicular volumes, particularly cHH patients ($P=0.019$). 23.1% of SLDP and 2.9% of HH patients had a family history of DP ($P=0.709$). 17.3% of SLDP compared to 34.6% of HH patients had classical symptoms of HH (e.g. micropenis, cryptorchidism, anosmia, renal or limb anomalies, $P=0.807$). Mean first recorded LH and inhibin B were also lower in HH patients, particularly in cHH patients ($P=0.005$, $P=0.002$). Mean genetic score of SLDP patients was lower at 3.00 ± 0.55 as compared to 3.47 ± 0.70 in HH patients ($P=0.008$). There were no significant differences identified in FSH, testosterone, AMH or bone age delay.
Discussion
This study identifies key phenotypic markers that help distinguish between SLDP and HH on first presentation, and that could be incorporated with genetic scoring to improve diagnostic accuracy. Further research into such an integrated framework or scoring system would be useful in aiding clinician decision-making and treatment optimisation.

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P718

Correlation between both serum and seminal fluid vitamin D levels and vitamin D receptor CDX polymorphism in male infertility

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Vitamin D (VD) now considered a steroid hormone, has been correlated with male reproductive disorders. The activity of VD is mediated through its receptor (VDR), distributed in various tissues including reproductive tissues. VDR polymorphism located in the promoter region of the gene, rs17883968 (Cdx2) G → A associated with transcriptional activity. The aim of this study was to assess both seminal and serum VD levels in a group of infertile patients ($n=87$, median: 34 years, range 20–55 years) vs control ($n=24$, median: 33 years, range 20–45 years) to establish the relation with Cdx2 VDR polymorphism. Subjects presenting known causes of infertility were excluded from the study. The patients were divided in three groups according to sperm count analysis: oligoasthenospermia, oligoterato-asthenospermia and azoospermia group. In this purpose, freshly collected blood was drawn from the subjects. Seminal fluid was harvested after 3–5 days of sexual abstinence. 25(OH) Vit. D serum and seminal levels were assayed using the electrochemiluminescence method according to the manufacturer's recommendations (Roche Diagnostics, Basel, Switzerland) with the RocheCobas E601 autoanalyzer. CDX polymorphism was evaluated through specific VDR gene PCR followed by digestion with the restriction enzyme Bpu10I (New England Biolabs). The VD serum levels was found to be low in the subjects infertile compared to the control group, and the analysis of the three groups of infertile vs. control shows differences Statistically significant for oligoasthenospermia ($P=0.0109$), oligoteratoasthenospermia ($P=0.0420$). No notable differences were observed in the seminal fluid. However, the VD levels were higher in seminal fluid than serum in all groups and a strong statistical significance was observed, suggesting the ability of reproductive tract to synthesize VD locally. VD levels were found to be significantly decreased in subjects with CDX- AA genotype especially in azoospermia ($P=0.0028$) and oligoasthenoteratospermia ($P=0.0198$). This study demonstrates a direct and positive relationship between serum VD level and overall semen quality. The results provide new insights into the involvement of the Cdx-2 polymorphism and VD deficiency in male infertility, providing genetic evidence for the role of the VDR in the development of male infertility. Taking into account the results, we highlight the important role of genetic changes at the VDR level associated with VD deficiency in male infertility.

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P719

The fertility status of patients with Cushing's disease under treatment

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Introduction
The main goal of treatment in Cushing's disease (CD) is to induce remission as well as to restore reproductive function. We aimed to evaluate the reproductive status of the female patients with CD encountered in sexually active patients after surgical with/without medical treatments.
Method
The retrospective data was obtained from the medical records of the 72 female patients diagnosed with CD at hospital registration system. The patients were contacted on 8/2022 by phone and were asked about their CD and reproductive histories. Two patients having a history of TAH-BSO, 15 individuals who could not be reached by phone, and three dead patients were excluded from the study.
Results
Six of the patients were single at the time of the research, so no further inquiries regarding fertility status were made. At the time of the diagnosis, 39 of the females were premenopausal. Thirty premenopausal patients were followed in remission. In terms of the number of pregnancies before CD diagnosis, 33 sexually active individuals had 72 pregnancy and 60 live births. Before CD diagnosis, two patients had attempted *in vitro* fertilization (IVF) once, and one patient had attempted IVF twice. Four IVF attempts resulted in three pregnancies and one live birth. Twenty four patients had no pregnancy loss, six patients had one pregnancy loss, and three patients had two pregnancy losses. During the post-treatment period, hypogonadism was detected in 12 of 33 premenopausal individuals following CD treatment. Six of the 33 patients were using contraception. Eleven patients wanted to get pregnant. Twenty seven contraceptive-free patients had a history of ten pregnancies, seven live births, and two pregnancy losses. Two patients experienced miscarriage once. Two (7%), one (%3.7), and one (3.7%) couples underwent IVF once, four and five times, respectively. The number of pregnancies and live births during the remission period of CD were reduced, while the frequency of miscarriage was the same.
Conclusion
While current therapies achieve remission in the majority of the patients, they do not contribute to the formation of adequate reproductive functions despite the improved infertility treatment procedures. Endocrinologists' and pituitary surgeons' incorrect assumption of the low possibility of achieving pregnancy rates even if remission is achieved, should be corrected, and refer patients with CD at the correct time without delay for assisted reproductive procedures if necessary.

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P720

Endocrine and Non-Endocrine Causes of Fatigue in Adults With Turner Syndrome: Cohort Study and Review of the Literature

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Background
Turner syndrome (TS) is a rare genetic developmental disorder characterized by gonadal dysfunction, short stature and heart defects, among others. Women with TS often suffer from severe fatigue, for which they are typically referred to endocrinologists. The diagnostic work-up is generally time-consuming and invasive, but it rarely solves the problem. To prevent the personal and financial burden of unnecessary diagnostic procedures, it is crucial to understand fatigue in TS. Therefore, in this study, we explored the association between fatigue and endocrine and non-endocrine comorbidities in a – for rare disorders – large group of TS women.
Design
Cross-sectional study.
Methods
170 genetically confirmed TS women who attended the TS reference center underwent a systematic health screening, including a structured interview, complete physical examination, biochemical measurements, perceived stress and fatigue questionnaires and additional tests when indicated.
Results
Median age was 32.6 years (IQR 23.9 – 41.4 years) and median BMI was 25.4 kg/m^2 (IQR 22.6 – 28.5 kg/m^2). One in three TS women experienced severe fatigue. Liver enzyme disturbances and body mass index were significantly associated with higher fatigue scores, while childhood growth hormone treatment was associated with lower fatigue scores. Perceived stress was highly correlated with fatigue ($\rho = 0.71$; $P<0.001$).
Conclusions
There was no association between fatigue and most endocrine and non-endocrine disorders, which implies that fatigue is only partly explained by somatic disorders. The high correlation between perceived stress and fatigue suggests that TS-specific neuropsychological processes may play an important role in the etiology of fatigue in TS women. We provide a practical algorithm for the endocrine, non-endocrine and psychological approach to fatigue in TS women.

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P721

In vitro exposure to the endocrine disruptor atrazine induces a pro-oxidant state and modulates mouse Sertoli cells metabolic support of spermatogenesis

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Introduction
Atrazine is one of the most widely used pesticides worldwide and a common contaminant in human drinking water. Atrazine is also a potent endocrine disruptor capable of causing a variety of negative health outcomes, including decreased testosterone production and infertility. Although harmful effects of atrazine on male reproductive health have been reported, little is known about its molecular mechanisms. Within the seminiferous tubules, Sertoli cells are responsible for ensuring a suitable environment for spermatogenesis, providing mechanical and nutritional support to germ cells. However, the cytotoxic and metabolic effects of atrazine on Sertoli cells remain unknown.
Aim of this study
In this work, we aimed to elucidate the effects of the endocrine disruptor atrazine on the nutritional support of spermatogenesis by studying its effect on the metabolic profile and mitochondrial function of Sertoli cells.
Materials and methods
Mouse Sertoli cells (TM4 cell line, $n=10$) were exposed to biologically relevant concentrations of atrazine (in µg/l: 0.3, 3, 30, 300 and 3000). After 24 h, cytotoxicity was accessed. The mitochondrial activity and total ROS production were accessed by JC-1 dye and CM-H_2DCFDA probe, respectively. FRAP assay was used to measure the antioxidant potential of culture media. Lactate dehydrogenase (LDH) protein levels were analyzed by Western Blot and the glycolytic function was evaluated by Seahorse XF Glycolysis Stress Test Kit.
Results
Despite no cytotoxicity was observed, our results show a decreased metabolic activity when cells were exposed to 300 µg/l and 3000 µg/l of atrazine for 24 h. Additionally, a dose-dependent decrease in the expression of LDH was observed after exposure. Although the mitochondrial function of Sertoli cells was not affected by atrazine, we observed a tendency for increased endogenous ROS production in the highest atrazine concentrations (300 µg/l and 3000 µg/l) associated with a decreasing trend in the antioxidant potential of the culture media in the same concentrations, suggesting a pro-oxidant status.
Conclusions
Our data suggest that atrazine interferes with the glycolytic metabolism of mouse Sertoli cells, by reducing oxidoreductase activity and LDH expression. Since lactate is the preferred energetic source for developing germ cells, the nutritional support of spermatogenesis may be compromised. In addition, our results suggest that atrazine may induce a prooxidant status, leading to increased ROS production and oxidative stress. Overall, the endocrine disruptor atrazine induces a pro-oxidant state and modulates Sertoli cells metabolic support of spermatogenesis which can compromise it and lead to male infertility.

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P722

Comparison of omentin (intelectin-1) expression and regulation in ovarian follicle cells from normal weight Large White and obese Meishan pigs

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Introduction
Omentin, also known as intelectin-1 (ITLN1), is a novel adipokine produced predominantly by visceral adipose tissue, which improves insulin sensitivity. Decreased levels of ITLN1 have been reported in the serum of obese and polycystic ovary syndrome patients, as well as in the serum and adipose tissue of obese Meishan (MS) compared to normal weight Large White (LW) pigs. However, the role of ITLN1 in female reproduction at different metabolic status is still unknown.
Aims and methods
This study aimed to 1) examine the mRNA (real-time PCR) and protein (Western blot) expression and immunolocalization (immunofluorescence) of ITLN1 in the ovarian follicles as well as its concentration in follicular fluid (FF, ELISA) at different days of estrous cycle (days 2-3, 10-12 and 14-16 of estrous) in LW and MS pigs; 2) determine the *in vitro* effect of gonadotropin (LH, FSH) and steroids (P_4, T, and E_2) on ITLN1 expression in ovarian follicular cells and its secretion to the culture medium in LW and MS pigs; 3) the involvement of extracellular signal-regulated kinase (ERK1/2) and phosphatidylinositol 3'-kinase (PI3K) signalling pathways in the regulation of ITLN1 expression in LW pigs. Statistical analysis was performed using a one-way analysis of variance and Tukey's test ($P<0.05$).
Results
We showed elevated ITLN1 expression in the ovarian follicles as well as its concentration in FF of LW compared to MS pigs; interestingly, in both breeds of pig, the level of ITLN1 increased with the progression of the estrous cycle. Immunofluorescence showed ITLN1 presence in granulosa, theca, cumulus cells, and oocytes. Both gonadotropins and steroids increased the level of ITLN1 in the ovarian follicle cells as well as in culture medium from LW pigs through kinases ERK1/2 and PI3K, while in MS pigs we observed only the stimulatory effect of LH and T on ITLN1 levels.
Conclusions
For the first time we demonstrated dependent on metabolism condition and the estrous cycle phase ITLN1 expression in the porcine ovarian follicles as well as its regulation by gonadotropins and steroid hormones through ERK1/2 and PI3K signaling pathways. Future studies will be necessary to understand the role of ITLN1 on ovarian function like steroid synthesis of animals with different metabolic states.
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P723

Early markers of metabolic disorders, such as leucin and isoleucine level and lipid accumulation product, should be considered as the potential additional criterium in PCOS classification

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Background
Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects reproductive age women and predispose to the development of metabolic disturbances. However, Rotterdam criteria, commonly used to diagnose and classify this disorder, do not include metabolic markers. Recent research has shown that several metabolic factors may play a role in PCOS pathogenesis. Branched-chain amino acids (BCAA) are the group of essential amino acids including leucine, isoleucine and valine and studies have shown that PCOS women have higher levels of BCAA compared to healthy individuals. LAP (lipid accumulation product) is an index combining waist circumference and triglycerides concentration that was found to be helpful in recognizing insulin resistance and predicting liver steatosis.
Methods
A group of 326 women: 209 diagnosed with PCOS and 117 healthy individuals, was included in the study. Multiple parameters were assessed, including anthropometrical, biochemical and hormonal ones; HOMA-IR and LAP were calculated using known formulas. The gas–liquid chromatography combined with tandem mass spectrometry was used to investigate BCAA level. PCOS women were grouped using Rotterdam criteria into four main phenotypes, which included: A-46, B-92, C-43 and D-28 individuals. Additionally, from the PCOS group, 46 women diagnosed with obesity were separated for further analysis. Subsequently, obese PCOS patients were classified as Metabolically Healthy (MHO) and Metabolically Unhealthy Obesity (MUO); these subgroups consisted of 27 and 19 age-matched individuals, respectively.
Results
Statistical analysis of metabolic parameters showed significant differences in BMI, HOMA-IR and total cholesterol level between PCOS phenotypes; however, fasting glucose, HDL, triglycerides, valine, leucine and isoleucine concentrations, as well as LAP do not differ in these subgroups. Comparison of MHO and MUO PCOS women, revealed that LAP, leucine and isoleucine concentrations were significantly higher among MUO subgroup: 101.98 ± 34.74 vs 55.80 ± 24.33 ($P<0.001$); 153.26 ± 22.26 vs 137.25 ± 25.76 nmol/ml ($P=0.04$) and 92.92 ± 16.09 vs 82.60 ± 18.70 nmol/ml ($P=0.02$), respectively. No significant differences in BMI, fasting glucose and HOMA-IR between MHO and MUO were found: 35.0 ± 4.8 vs 36.1 ± 4.6 kg/m2 ($P=0.59$); 88.0 ± 6.0 vs 87.73 ± 6.28 mg/dl ($P=0.67$); 3.36 ± 1.70 vs 4.17 ± 1.77 ($P=0.1$), respectively.
Conclusions
PCOS phenotypes distinguished with Rotterdam criteria represent the differences between patients according to ovulatory and androgen excess symptoms. However, to better identify patients at risk of metabolic disorders, a new classification is needed. Leucine and isoleucine concentrations, as well as lipid accumulation product, should be taken into consideration as metabolic factors that might be included in PCOS classification since they are helpful in differentiation of 'metabolic health'.
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P724

Effects of testosterone therapy on erythrocytosis and prostate adverse events in obese males with functional hypogonadism and type 2 diabetes

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Aims
Testosterone therapy (TTh) has been postulated to increase the risk of prostate adverse events (PAEs) and erythrocytosis, risk further exacerbated in high-risk obese patients with type 2 diabetes (T2D) and functional hypogonadism (FH). We investigated safety aspects of TTh in obese males with FH and T2D by observing the incidence of PAEs and erythrocytosis and determining when statistically significant difference from the baseline manifests in hematocrit (Hct) and prostate-specific antigen (PSA) levels.
Materials and Methods
Fifty-five obese men with FH and T2D participated in a two-part, prospective observational clinical study (first year: double-blind, randomized, placebo-controlled trial employing testosterone undecanoate; second year: open-label follow-up with all participants receiving TTh). Outcomes were assessments of Hct and PSA levels at the baseline, and 3, 6 and 12 months into each of two years of the study.
Results
No adverse cardiovascular events or PAEs were observed. Hct first increased at statistically significant level from the baseline after 3 months of TTh in group T and after 6 months of TTh in group P. Individual Hct values for all participants remained below 0.52 throughout 2-year course of the study. PSA increased from the baseline in both groups within 3-6 months of trial start regardless of intervention applied (placebo or TTh). 52 patients never exceeded PSA level of 4.0 μg/l nor experienced year-on-year PSA increase $>$ 1.4 μg/l. No subject ever reached supraphysiological concentration of total testosterone.
Conclusions
Our results show that TTh may be safe in obese males with FH and T2D.
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P725

The Role of Testosterone Treatment in Patients with Type 2 Diabetes Mellitus: Results from A Meta-Analysis Study

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Introduction
type 2 diabetes mellitus (T2DM) and hypogonadism are common conditions afflicting the aging male, often present together. The specific role of testosterone (T) replacement therapy (TRT) on glycometabolic profile and body composition, particularly in patients with T2DM, is still the object of an intense debate. The aim of the present study is to meta-analyze the role of TRT in T2DM considering all placebo and non-placebo-controlled randomized clinical trials (RCTs).
Methods
an extensive Medline, Embase and Cochrane search was performed. We did not employ search software but hand-searched bibliographies of retrieved papers for additional references. All RCTs studies investigating the impact of TRT on glycometabolic outcomes without any restriction were included.
Results
overall, 12 studies were available including 684 patients with a mean follow-up of 38.4 weeks. These trials differ in basal TT levels and type of T preparation used. In addition, only 10 were placebo controlled Patients with impaired fasting glucose were characterized by a 3 nmol/l lower level of total testosterone when compared to controls. Similarly, impaired fasting glucose was associated with a 1.8-fold increased risk of hypogonadism, when compared to subjects with normal glucose levels. Secondary hypogonadism was two times higher in subjects with impaired fasting glucose when compared to rates observed in the general population. Testosterone replacement therapy was able to improve body composition, insulin resistance, and glucose profile both in impaired fasting glucose and type 2 diabetes mellitus whereas its role on body weight, lipid profile, and sexual function was less evident.
Conclusions
The overall data analysis indicates that TRT favorably affects glycemic control in diabetic subjects reducing fasting glycaemia, HbA1c and HOMA index and decreasing triglyceride levels and fat mass. All these differences were confirmed when only placebo-controlled studies were evaluated, with the exception for HbA1c decrease, where only a trend towards a decrease was apparent. Conversely no effects on TRT on erectile function was observed.

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P726

The impact of pharmacological treatments on oxidative stress, inflammatory parameters and semen characteristics

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Introduction
Although the pathogenic mechanism is not completely understood, pharmacological treatments could negatively affect seminal parameters. The analysis of inflammatory (i.e. cytokines) and oxidative stress parameters represent a new tools to investigate the causes of idiopathic male infertility. The aim of this study was to evaluate the impact of medications on oxidative stress, inflammatory parameters and semen characteristics in male with idiopathic infertility.
Materials and Methods
In this observational, case-control, clinical study 50 men with idiopathic infertility, referring to the Endocrinology-Andrology Unit of Sant'Andrea Hospital – 'Sapienza' University of Rome, from October 2017 to June 2018 were enrolled. Of them, 38 subjects (study group) were on pharmacological treatment from at least three months and 12 subjects were enrolled as a control. The study group were clustered according to the medications (Group A: antihypertensive, n.10; Group B: thyroxine, n.6; Group C: chronic anti-inflammatory, n.13; Group D: miscellaneous, n.6; Group E: lipid-lowering agents, n.4). Semen analysis were performed according to WHO 2010 guideline. Interleukins (IL)-10, IL-1beta, IL-4 as anti-inflammatory cytokines, IL-6, TNF-alpha as pro-inflammatory, and IL-1alpha, as a marker of testicular function, were determined using a solid phase sandwich immunoassay. The d-ROM test was assessed through a colorimetric determination of reactive oxygen metabolites and measured by a spectrophotometer. Beta-2-Microglobulin and Cystatin-C, were measured with an immunoturbidimetric analyzer.
Results
No difference between study and control group for age and macroscopic and microscopic semen characteristics were found. The same result was obtained after clustering and comparing the study group according to the drug categories. IL-1 alpha and IL-10 were significantly lower in the study group compared to control. After clustering the study group, IL-10 was significantly lower in groups A, B, C and D compared to control group. Furthermore, a direct correlation between IL-1alpha, IL-10 and TNF-alpha and leukocytes was found. Conversely, a statistically significant inverse correlation between IL-4 and sperm concentration, and between beta-2 Microglobulin and total sperm number were highlighted.
Conclusions
This study represents a first attempt to understand how drugs belonging to different categories could affect the properties of semen. Although the sample size was not large, the data suggests a correlation between the use of medications and inflammation. This could clarify the pathogenic mechanism of action for several pharmacological classes on male infertility, which is not completely known. Further studies on larger populations are needed to investigate the possible role of the various drug categories on male fertility.

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Resistin as A New Regulator of Luteolysis: *in Vitro* Effect of Resistin on Proliferation, Apoptosis, and Autophagy in Porcine Luteal Cells

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To maintain proper fertility the balance between formation and luteolysis of corpus luteum (CL) are necessary and strictly controlled events in female reproduction. Degeneration of CL is correlated with apoptosis and autophagy as well as connected with decreased progesterone (P4) level. Resistin is a new key player in the regulation of luteal cells function; our previously study showed that resistin have negative effect on P4 synthesis. Thus the aim of the present study was to investigate the effect of resistin on proliferation, apoptosis, and autophagy of porcine luteal cells and involvement of mitogen-activated kinase (MAP3/1), protein kinase B (AKT), and signal transducer and activator of transcription 3 (STAT3) in these processes. Porcine luteal cells at the middle luteal phase were incubated with resistin (0.1-10 ng/ml) for 24 h to 72 h and cells proliferation was assessed by alamarBlue or MTT assay. Then, the time-dependent (24 h to 72 h) effect of resistin (1 ng/ml) on the transcript and protein level of proliferation: proliferating cells nuclear antigen (PCNA), apoptosis: caspase 3, BCL2-like protein 4 (BAX), B-cell lymphoma (BCL2), and autophagy: beclin1, microtubule-associated protein 1A/1B-light chain 3 (LC3), lysosomal-associated membrane protein 1 (LAMP1) markers were measured by real-time PCR and Western blot, respectively. We noted that resistin stimulated luteal cell proliferation with no effect on caspase 3, increased BAX/BCL2 ratio and enhanced the initiation of autophagy, which promotes the maintenance of luteal function rather than its luteolysis. Besides, using pharmacological blockers of MAP3/1 (PD98059), AKT (LY294002), and STAT3 (AG490) we observed that the effect of resistin was downregulated to the control level in proliferation and by activation MAP3/1 and STAT3 in autophagy. Summarizing, our results indicated that resistin is a new regulator of female reproduction by direct effect on CL regression, formation and maintenance of luteal cell function. It may be a future therapeutic target in luteal cells deficiency treatment leading to enhanced numbers of healthy pregnancies. However, *in vivo* experiments are necessary to confirm this hypothesis.
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P728

Polygenic Score for Dizygotic Twinning in Mothers of Spontaneously and Artificially Conceived Twins and Singletons

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Spontaneous dizygotic (DZ) twinning results from a double ovulation and runs in families indicating a genetic component. Endocrinology studies in mothers of DZ twins observed higher levels of follicle stimulation hormone (FSH) and *FSHB* was, together with *SMAD3*, one the first loci identified as genome wide significant in genome-wide association studies (GWAS) of having DZ twins. Several additional loci were recently found that indicate genes involved with female endocrinology and fertility such as *FSHR*, and *GNRH1*. A polygenic score (PGS) for spontaneous DZ twinning, which summarises an individual's genetic risk, explained ~1.5% of the phenotypic variance when comparing mothers of spontaneously conceived DZ twins to controls. Here we compare the PGS in mothers of spontaneously conceived DZ twins with other twin mothers in the Netherlands twin register (NTR) and in the Norwegian Mother, Father and Child Cohort Study (MoBa). In the NTR, we contrast the PGSs and several demographic and lifestyle traits in four groups ($n=34.895$): those who conceived DZ or monozygotic (MZ) twins spontaneously, and those who conceived DZ or MZ twins through artificial reproductive techniques (ART) with logistic regression. Mothers of spontaneously conceived DZ twins differed in maternal age, body composition, parity and smoking behavior compared to the other groups. The PGSs ($n=4.498$), both corrected and uncorrected for these demographic and lifestyle traits, were higher in mothers of spontaneously conceived DZ twins compared to all other twin mothers, whereas the PGSs of the other three groups did not differ. We are currently conducting the PGS analyses in mothers of twins and singletons from MoBa ($n=$approximately 95.000 mothers). Our study shows that mothers of spontaneously conceived DZ twins are genetically different, and also differ in demographics and lifestyle traits compared to the other groups of twin mothers. Further endocrine, metabolomics and gene expression studies are required to help elucidate underlying processes.

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P729

Sex hormones as independent predictors of severe COVID-19 in patients with SARS-CoV-2 infection

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Introduction
The SARS-CoV 2 pandemic has resulted in millions of deaths worldwide. It has been suggested that sex steroids may be involved in the prognosis of the disease.
Material and methods
Male patients diagnosed with SARS-CoV-2 infection admitted to the Marqués de Valdecilla University Hospital (Spain). Testosterone, androstenedione, estradiol, DHEA and DHEAS were determined in the first 24 h of admission and severe COVID was defined as mortality or ICU admission. For each biomarker, area under curve (AUC) and its 95% CI were estimated by using ROC curves. Levels of biomarkers were ordinal categorized in tertiles (T1, T2 and T3), and as association measure odds ratios (OR) with their 95% CI adjusted for age, BMI, smoking, renal disease and diagnosis of diabetes.
Results
Data were obtained from 98 patients: mean age 63.65 ± 15.53y; 54/98 showed severe covid (55.1%). Predictive accuracy of biomarkers was: AUC total testosterone 0.72; 95% CI (0.61–0.82); AUC androstenedione 0.59; 95% CI (0.47-0.71); AUC estradiol 0.70; 95% CI (0.60-0.80); AUC DHEA 0.75; 95% CI (0.65–0.85); AUC DHEAS 0.66; (0.55–0.78). With regard to the risk of severe COVID for the patients at the lower tertil (T1) in comparison with the higher tertile (T3), except for estradiol in which the lower tertile was the reference, the associations were: OR (total testosterone) = 3.90 (1.38-11.04); OR (androstenedione) = 2.20 (0.77-6.30); OR (estradiol) = 4.62 (1.60-13.35); OR (DHEA) = 6.17 (1.97-19.35) and OR (DHEAs) = 3.90 (1.38-11.04). The results were not affected after adjusting for age, BMI, smoking, renal disease and diagnosis of diabetes.
Conclusion
Our results suggest that sexual steroids are independent predictors of severe COVID-19 (mortality or ICU admission) in patients with SARS-CoV-2 infection. The predictive ability discriminated by the AUC of the ROC curve is higher for testosterone and DHEA.

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P730

Influence of Obesity on Medically Assisted Reproduction Techniques

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Introduction
Evidence has suggested a relationship between female obesity and the outcomes of medically assisted reproduction techniques (MRT); however, the evidence regarding male obesity is still scarce and discordant.
Aim
Evaluate the influence of female and male obesity on the results of MRT.
Materials and methods
Retrospective analysis of 2159 couples, with and without obesity, submitted to the first treatment of medically assisted reproduction. Considering each individual of the couple, four groups were defined according to sex and body mass index (BMI) (non-obese group with BMI <30 kg/m^2 and obese group with BMI ≥ 30 kg/m^2).
Results
Among female individuals, 235 were obese (10.9%). Median age was similar between groups with and without obesity (35 years (31-37) vs 34 years (31-37), $P=0.541$). Ovarian stimulation was mostly performed with a short cycle with an antagonist in both groups (75.1% vs 68.6%, $P=0.674$) and *in vitro* fertilization was the most frequent technique in both groups (60.9% vs 66.9%, $P=0.086$). The obese group had a lower number of mature oocytes (4 (2-7) vs 5 (2-8), $P=0.015$) and of fertilized oocytes (2 (0-4) vs 2 (0-5), $P=0.026$). The fresh embryo transfer rate was similar between groups (50.2% vs 54.8%, $P=0.119$), as well as the probability of pregnancy (31.4% vs 38.3%, $P=0.103$). Among male individuals, 336 were obese (15.6%) and median age was similar between groups (36 years (33-39) vs 35 years (32-39), $P=0.357$). No differences were observed in the several parameters evaluated on the semen analysis or in the results of MRT, namely in the number of embryos obtained, transfer rate or pregnancy.
Conclusions
In this population, female obesity influenced the number of mature and fertilized oocytes. We believe that the lack of statistically significant difference in the rate of freshly transferred embryos between the female groups is related to the lack of fresh transfer in several patients due to the risk of Ovarian Hyperstimulation Syndrome. The analysis of frozen embryo transfer data would have been important for a better characterization of the embryo transfer rate in these groups. In this study, there does not seem to be a relationship between male obesity and sperm analysis parameters or the success of MRT.

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P731

Bilateral ovarian mass due to primary hypothyroidism - a case report

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Introduction
The triad of primary hypothyroidism, precocious puberty and delayed bone age in children with cystic ovarian enlargement constitutes the syndrome of van wyk grumbach. Commonly reported as a rare complication of hypothyroidism in children, there are only a few case reports in adult population. Herewith, we are reporting the case of a 22-year-old hypothyroid lady, who presented with bilateral ovarian cysts. Considering hypothyroidism, a high risk for surgery, thyroxine dose was optimised; to see that the cysts started shrinking in size and eventually disappeared.
Case
22-year-old lady, with no known comorbidities, presented with complaints of lower abdominal pain for 1 week. On examination, there was a mass felt in the left iliac region, reaching up-to the umbilicus. It was non-tender and non-ballotable

with cystic consistency. USG Abdomen showed bulky uterus with multiseptated cystic lesions in the adnexa, with no significant vascularity or solid components. It was succeeded with an MRI abdomen, which confirmed the same. There was age lobulated septate thin-walled cystic lesion in the right ovary measuring 13.5 x 8.1 x 6.9 cm, and a lesion in the left ovary measuring 7.3 x 6.4 x 6.5 cm, with probable haemorrhagic content. CA-125 was also found to be elevated. Though non-specific, with multicystic ovarian lesions and elevated CA-125 in a young lady, the possibility of an ovarian neoplasm was thought of and she was planned for laparoscopic ovarian cystectomy. On pre-operative evaluation, TSH was found to be significantly elevated – 65.42 mcIU/ml. Endocrinology consultation was sought and she was started on Thyroxine supplementation. Surgery was postponed in view of peri-operative morbidity, and she was discharged. She was followed-up and thyroxine dose was optimised in subsequent visits. Repeat imaging showed complete resolution of mass after 6 months.

Conclusion

Multiple ovarian cysts in a young lady can be indicative of an infection or malignancy, but at times can be due to benign systemic conditions like hypothyroidism. Prompt treatment of hypothyroidism made the ovarian cysts to disappear, which otherwise would have resulted in a major futile surgery.

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P732

Impact of chromium picolinate on testicular steroidogenesis

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Low testosterone levels are one of the causes of male infertility since testosterone is a crucial hormone for the regular functioning of the male reproductive tract. Testosterone is produced by Leydig cells (LC) in a process called testicular steroidogenesis, and if these cells are injured in any way, then the steroid production may be compromised. Endocrine Disrupting Chemicals (EDCs) are a group of substances that disturbs hormonal signaling. Their chemical nature and mode of action are diverse and chromium, a heavy metal, has been classified among EDCs. Trivalent chromium (Cr(III)) is one form of chromium controversially considered an essential metal. Chromium (III) picolinate (CrPic3) is a Cr(III) organic salt that is used as a nutritional supplement due to its antidiabetic properties, among others, despite the controversies surrounding the safety of Cr(III). The main effect identified in LC was the inhibition of enzymes involved in steroidogenesis, while in other somatic cells, CrPic3 appears to induce mutagenesis and apoptosis. The production of testosterone seems to be affected by this supplement, however we found conflicting results on this subject. In this work we aimed to evaluate whether CrPic3 displays cytotoxic effects in the murine LC line BLTK1, to understand if it could affect this population of cells and the production of testosterone. The cytotoxicity assays preformed with 5 different concentrations of CrPic3 (0.1, 1, 10 and 100 μM) showed that this supplement does not significantly affect the proliferation, viability of cell membrane integrity of these cells. These results suggest that CrPic3 the LC themselves are not harmed by the supplement, however our ongoing work is now focused on understanding if testosterone production is compromised.

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P733

Periodic Assessment of Biochemical-Hematological Changes in A Series of Transgender Men After 1 Year of Gender Affirming Therapy

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Introduction

During gender affirming therapy in transgender men (TXM), androgens are administered at escalating doses. As therapy progresses, changes in various analytical parameters occur that may be of potential use in establishing a personalised androgen dosage and avoiding deleterious effects of the medication. The aim of our study was to study the evolution of different parameters throughout the course of gender affirming therapy.

Material and methods

The study was conducted in a cohort of 20 TXM. Treatment was initiated with 25 mg/month of IM testosterone cypionate. Every three months the dose was increased by 25, 50 and 150 mg/month until the maximum dose of 250 mg/month is reached after a year. Samples at 3, 6, 9 and 12 months were analysed by spectrophotometric and automated immunoassay techniques on Snibe Maglumi and Siemens Atellica platforms. Friedman's test and Wilcoxon pairwise comparisons were performed in SPSS25.0.

Results

The most significant results are summarised in the following tables: No significant differences were found for lipid profile, HbA1c, bilirubin, urea, cortisol, insulin, androstenedione, gonadotrophins and oestradiol. While LH, oestradiol and HDL tended to decrease and triglycerides, cholesterol and urea tended to increase, given the sample size, this was not significant. However, we did obtain significance for haematocrit, haemoglobin, FAI, creatinine and both free and total testosterone.

Conclusions

Several of the parameters analysed change as gender affirmation therapy progresses. Haematocrit is the earliest change. The first significant changes occur after 6 months of treatment. It would be of interest to study a cut-off point for each parameter to allow dose adjustment according to the changes found. The study should be completed when a larger number of subjects in our study who are currently in evolution complete one year of therapy.

Table 2 (Abstract P733) Friedman results and pairwise comparison with Wilcoxon test for hormonal parameters:

	Testosterone	Free testosterone	FAI	DHEAS
Significance Friedman test	$P<0.001$	$P<0.001$	$P<0.001$	$P=0.024$
First time at which differences are found with basal	$t_{0\text{-}6}$: $P=0.003$	$t_{0\text{-}6}$: $P=0.003$	$t_{0\text{-}6}$: $P=0.004$	$t_{0\text{-}3}$: *$P=0.033$

* Taking into account the Bonferroni adjustment it would not be significant for any time.

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P734

A retrospective observational study of thyroid function throughout a pregnancy and its effects on the fetus and the mother

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Table 1 (Abstract P733) Friedman results and Wilcoxon pairwise comparison for biochemical parameters:

	Creatinine	GGT	ALP	Hematocrit	Haemoglobin	PSA
Significance Friedman test	$P<0.001$	$P<0.003$	*$p=0.036$	$P<0.001$	$P<0.001$	$P=0.010$
First time at which differences are found with basal	$t_{0\text{-}6}$: $P=0.004$	$t_{0\text{-}6}$:* $P=0.035$	$t_{0\text{-}9}$: $P=0.010$	$t_{0\text{-}3}$: *$P=0.052$	$t_{0\text{-}6}$: $P=0.001$	$t_{0\text{-}9}$: *$P=0.023$

* Non significant with Bonferroni adjustment ($P>0.01$), although a clear trend can be observed.

Introduction
Maternal thyroid function is put under stress during pregnancy. Thyroid disorder is very common among expectant mothers. 10% of pregnancies have subclinical hypothyroidism. Anemia, low birth weight, and neonatal mental retardation are among side effects of hypothyroidism during pregnancy.
Objective
The primary and main objective is to evaluate the results for pregnant women with abnormal thyroid profiles, both for the mother and the fetus. This study is important because it provides evidence of the link between hypothyroidism and harmful consequences on both mother and fetus.
Method
At Patna Medical College, this retrospective observational study was conducted. Informed consent was obtained from the 190 prenatal women participating in this study, who were in their third trimester and had singletons. Regardless of their age, parity, place of residence, or social level, women were chosen. All pre-existing medical conditions, multiple pregnancies, thyroid disorders known to exist, and multiple pregnancies were prohibited. Routine hematological parameters and T3, T4, and TSH estimates were done. Patients with abnormal thyroid profiles were then evaluated for issues that could affect the mother or the fetus. The primary study variables included menstruation pattern, recurrent abortion, history of infertility, family history of thyroid disease, hemoglobin level, and fetal outcome. SPSS software was used to analyze the data for statistical correlation.
Results
Subclinical hypothyroidism, overt hypothyroidism, and subclinical hyperthyroidism occur in 5.5, 3.4, and 1.4% of individuals, respectively, according to the prevalence of thyroid disorders, which is 10%. Anemia was seen in 26.2% of women with subclinical and overt hypothyroidism, and it was substantially correlated with hypothyroidism ($P=0.007$). In terms of foetal outcome, hypothyroidism was statistically linked with LBW 31.5% ($P=0.002$), NICU admission 42.0% ($P=0.001$), and low APGAR Score (21.0%, $P=0.041$). Mothers with hypothyroidism had a 4.6, 6.2, 0.13, and 3.63 times higher risk of anemia, low birth weight, NICU hospitalizations, and a low APGAR score than women who are euthyroid.
Conclusions
In the third trimester of pregnancy, subclinical hypothyroidism is present in 5.5% of women. Significant correlations exist between hypothyroidism and anaemia, pre-eclampsia, high caesarean rates, and infant morbidities.

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P735

Biological variation data of anti-Müllerian hormone and androstenedione among women of reproductive age

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Introduction
Biological variation (BV) data describe the variability of clinically important measurands around homeostatic set points within subjects (CVI) and between subjects (CVG). The availability of well characterized data enables the interpretation of laboratory results in clinical settings and can also be used to define analytical performance specifications. The aim of this study was to deliver BV estimates for anti-Müllerian hormone (AMH) and androstenedione among women of reproductive age.
Materials and Method
In total, 40 healthy women of reproductive age (19–42 years) were bled for three consecutive menstrual cycles, on the 2nd or 3rd day of the cycle. Sera were stored at -80°C before analysis. Analyses for each patient were performed in duplicate within a single run on the Roche Cobas analyser e801 (Roche Diagnostics GmbH, Mannheim, Germany) by electrochemiluminescence immunoassay. The BV estimates with 95% CIs were obtained by CV-ANOVA, after analysis of variance homogeneity and outliers.
Results
The CVI and CVG for AMH were 15.3% and 67.7%, respectively. Analytical variation (CVA) was calculated as 4.6%. The CVI and CVG for androstenedione were 17.9% and 41.2%, respectively. CVA was calculated as 2.1%.
Conclusion
In cycling women, the variability in AMH should be considered by clinicians, especially if a result is close to a clinical cutoff. The serum AMH CVI obtained by this study specifies more stringent analytical performance specifications than previously identified. The added value of this research is the availability of updated BV data, in the case of androstenedione that were not previously published.

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P736

The Impact of Covid-19 Lockdown on Pubertal Onset in A Second Level Center

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Background
As of December 2019, the COVID-19 pandemic has spread rapidly, therefore Governments from all over the world promoted a strategy of social confinement through a general lockdown in order to contain it. During the months following its introduction, many studies reported a significant increase in the incidence of idiopathic central precocious puberty (CPP) throughout several countries, especially in girls.
Purpose
The aim of our study was to compare the incidence of idiopathic CPP before and after the onset of COVID-19 lockdown (which started on March 9th 2020 in Italy) among the medical records of patients who were referred to our highly specialized Endocrinological Center from 2014 to July 2021; we also aimed to identify any potential differences in either anamnestic, clinical, biochemical or radiological characteristics between patients in whom CPP occurred before and after the beginning of lockdown.
Methods
We retrospectively analyzed the characteristics of 51 patients with idiopathic central precocious puberty: 32 with pre-lockdown CPP onset and 19 with post-lockdown CPP onset. Firstly, we compared the incidence of the disease between the two time periods. Secondly, we collected information from patients' medical history, physical examination, baseline and dynamic hormonal assessment, bone age, and pelvic ultrasound around the time of diagnosis and compared such information between the two groups.
Results
We registered an almost threefold increase in CPP incidence in the 2020-2021 period compared to the previous six years. We also found that post-lockdown patients had a trend for lower delta LH percentage value (P 0.0633) and for an earlier diagnosis in terms of both chronological age at diagnosis (P 0.0628) and days between the onset of first pubertal signs and diagnosis (P 0.0762) compared to pre-lockdown patients. Furthermore, post-lockdown patients also had lower delta-4-androstenedione levels (P 0.0244) and mothers with an older age at menarche (P 0.0078).
Conclusions
Our study confirmed a significant increase in the incidence of CPP in the post-lockdown period. Moreover, taking into account both the positive correlation that exists between maternal age at menarche and the timing of pubertal onset of children, and the fact that the mothers of post-Covid patients had menarche significantly later than those of pre-Covid patients, our results suggest that the influence of genetics in determining the timing of pubertal onset of Post-Covid patients has been scaled back in favor of a stronger environmental influence (the lockdown itself).

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P737

Insulin-like growth factors: possible players regarding male fertility

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Infertility affects about 15% of couples, and, among these, 50% are related to the male factor. Male infertility can be caused by intrinsic factors, and these may either directly or indirectly affect gamete and testicular development as a consequence of endocrinopathies. In that sense, research regarding the involvement of endocrine hormones, particularly of nutritional status-linked hormones, in the male reproductive system has increased over the years. In fact, the rise on the incidence of metabolic diseases is positively associated with a decrease in fertility rates, suggesting that nutritional status-linked hormones may play a role in the crosstalk between both conditions. Among the nutritional status-linked hormones, little is known concerning the role of insulin-like growth factors for several facets of testicular development, spermatogenesis, and steroidogenesis. IGF-1 was found to be expressed in multiple testicular cells and some germ cells, being the Sertoli cells their main source in the seminiferous tubules. *IGF-2* mRNA has been found in human spermatozoa and is believed that IGF-2 is possibly produced by other cells of the male reproductive system, such as germ cells. However, the roles of both IGF-1 and IGF-2 for the male reproductive health and fertility outcomes remain poorly understood. Hence, the main goal of this work was to understand the contribution of IGF-1 and IGF-2 on male fertility. For that purpose, we identified and quantified the expression of *IGF-1* and *IGF-2* mRNA in spermatozoa samples of men ($n=111$) that underwent medically assisted reproduction (ART) treatments, through RT-PCR and RT-qPCR, respectively. We were able to identify for the first time, to the best of our knowledge, the expression of *IGF-1* mRNA in human spermatozoa. In addition, we also positively identified the expression of *IGF-2* mRNA in human spermatozoa. Further studies will disclosure the potential association between *IGF-1* and *IGF-2* mRNA expression and ART outcomes. The discovery of the expression of both IGF-1 and IGF-2 in human spermatozoa also opens the path for future studies concerning the role of nutritional status-linked hormones for male fertility and ART outcomes.

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P738

46, XX male (SRY positive): recalling a clinical case

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Introduction
XX male syndrome is a disorder of sex development associated with a 46, XX karyotype and is characterized by such features as: small testes, hypergonadotropic hypogonadism, male external genitalia, gynecomastia and azoospermia. The estimated prevalence is 1/20.000 males. Gender role and gender identity are reported as male. Identification and subsequent treatment is necessary to avoid the manifestations of testosterone deficiency.
Clinical Case
23 year old male presented to our medical appointment manly due to a history of erectile dysfunction but also presented with loss of libido, bilateral gynecomastia, infertility and showed signs and symptoms of clinical depression. He had no relevant family history. In the physical examination the patient had a weight of 70 Kg, normal development of secondary sexual characteristics and presented with a bilateral testicular atrophy with a volume of 6ml/testis. Blood analysis showed: LH 11.04 mUI/ml [Reference range (RR) 1.3-12.9], FS 30.81 mUI/ml (RR 0.9-15); Free testosterone 1.56 ng/ml (RR 2.7-10,7) and total testosterone 7,6 pg/ml (RR 2.7-10.7). There were no findings on the brain MRI. There were no other alterations in the US besides the atrophy. The karyotype test revealed the following: 46,XX. ish ins(X,Y)(p2;q11.2)(SRY+). The patient promptly started on testosterone with meaningful improvement of is libido, erectile dysfunction and return of LSH, FH and testosterone to levels within range. The bone densitometry reported an osteopenia and the spermiogram revealed an azoospermia. Medically assisted reproduction was initiated but the patient renounced it after a while. Until this day, the patient hasn't had any relevant clinical problem since the beginning of the treatment with testosterone.
Discussion
We present a clinical case of a male with an XX male syndrome positive for SRY gene. This is due to a Y to X translocation during meiosis and SRY is the main driver to testes formation. Our patient presents with an array of classical signs and symptoms and although it is reported that infertility is mainly the first recognisable problem, for our patient, erectile dysfunction was the main cause for seeking medical attention. Obstructive azoospermia was ruled out after performing US.
Conclusions
In these patients we should performed an adequate screening to set the better treatment depending on the phenotypic characteristics and be vigilante for any morbidity related to testosterone deficiency. The follow up by a multidisciplinary approach is ideal, especially if the patients seeks fertility options.

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P739

Experiences and expectation of young women with PCOS and their mothers: A Qualitative study in India

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Women diagnosed with polycystic ovarian syndrome (PCOS) experience several physiological (weight gain, hirsutism, acne) and psychological challenges (emotional distress, anxiety, shame). This is particularly apparent in India where PCOS intersects with gender and patriarchal notions of womanhood (interfering with one's marital prospects, compromising one's ability to procreate). A young woman's first source of support, therefore, is usually their mother. In India, a mother plays a pivotal role in managing and responding to one's outer, social world. However, little is known about the communication and coping efforts among Indian young women and their mothers with regard to the former's diagnosis and lived experiences of PCOS.
Objectives
This study aimed to understand the experiences of coping with PCOS-related challenges and communication between young women diagnosed with PCOS and their mothers in India
Methods
Semi-structured interviews were conducted with 12 mother-daughter pairs (total $n=24$; mean age of daughters = 22.4 years and mean age of mothers = 49.5 years). The individual, telephonic, audio-recorded interviews explored each respondent's experiences of managing PCOS-related symptoms, responses of their wider social network, concerns regarding the PCOS, and how they were communicating with their counterpart (i.e., mother or daughter). All interviews were all conducted in English and transcribed verbatim. The interviews were analysed using thematic analysis.
Results
Three themes were identified: (1) emotional turmoil and the emotional impact of having PCOS: how mothers and daughters felt about the PCOS-related symptoms and social reception of PCOS, (2) coming to terms with and adapting to the condition: mothers' and daughters' individual and collaborative responses to PCOS management, and (3) need for (empathic) communication between the mothers and daughters.
Discussion and conclusion
These findings indicated that both women with PCOS and their mothers experienced immense emotional turmoil, with the former describing feelings of shame and the latter feelings of worry. Mothers played a crucial role in aiding their daughters in lifestyle management, although mothers preferred attempting at multiple alternate remedies while daughters wanted to adhere to the physician prescribed management choices. The dyads reported a need for effective empathic communication between one another, particularly about lifestyle management. These findings highlight the need for (1) physicians to include mothers in PCOS-related discussions in their daily practice, (2) communication skills interventions for mothers and daughters, and (3) community outreach so as to improve sensitivity and awareness to the psychological aspects of having PCOS in India.

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P740

Improving detection of rare overgrowth syndromes among patients referred to the endocrinology ward for treatment of acromegaly

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Background
A common request at an endocrine outpatient clinic is to rule out acromegaly in a patient with acromegaloid features. It is important to do so, since the excessive excretion of growth hormone can result in various serious comorbidities. But when growth hormone-IGF-1 axis abnormalities are excluded, the physician faces

a diagnostic dilemma. Here we provide a systematic approach to these patients.
Methods
We present a case series of patients visiting our outpatient clinic for 'acromegaly', from presentation to diagnosis. We describe the diagnostic challenges and illustrate the added value of multidisciplinary treatment, initiated once patients were diagnosed with overgrowth syndromes. Additionally, we conducted a systematic review of the literature on overgrowth syndromes.
Results
The patients presented with acromegaloid characteristics without growth hormone/IGF-1 axis abnormalities. Endocrine and genetic work-up ruled out acromegaly and revealed mutations in *CHD8*. Neuropsychological assessment revealed a mild intellectual disability in one of the patients, which had remained unnoticed for years due to relatively strong verbal performance. To initiate ID support, the patient was referred to the physician for intellectual disabilities. Based on our own expertise in combination with the existing literature, we made an algorithm to improve diagnostics and management of adults with overgrowth syndromes. Due to their physical and neuropsychological problems associated with some overgrowth syndromes, multidisciplinary care is often necessary.
Conclusions
When a patient presents with acromegalic features in the presence of normal IGF-1, the diagnosis of overgrowth syndromes should be considered as underlying condition. As overgrowth syndromes may be associated with neurodevelopmental delay, we recommend to screen for mild ID and refer patient for multidisciplinary management to prevent the complications of undiagnosed ID.

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P741

Functional hypogonadism and prevalence of decreased total testosterone level in type 2 diabetic male patients

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Functional hypogonadism and prevalence of decreased total testosterone level in type 2 diabetic male patients
Background
Approximately 50 % of older males with obesity and type 2 diabetes, exhibit low total testosterone levels, many also signs of hypogonadism. Functional hypogonadism negatively affects glycemic control, exacerbates early cardiovascular complications, causes lower bone mineral density, erectile dysfunction, reduces lean body mass, and accelerates the accumulation of visceral fat. We aimed to determine the prevalence of decreased total testosterone level type 2 diabetic males in Slovenia.
Research design and methods
We presents the results of cross-sectional study in male patients with type 2 diabetes and obesity, with goal to assess prevalence of decreased total testosterone level. Participants were inquired to answer the The Aging Males' Symptom (AMS) scale questionnaire. Functional hypogonadism was diagnosed as a biochemical deficiency of circulating testosterone levels (total testosterone below 11 nmol/l and free testosterone below 220 pmol/l) on at least two separate morning measurements after an overnight fast.
Results
165 patients were included in this cross-sectional study. 87 patients exhibited decreased total testosterone level (below 11 nmol/l) while 78 had normal level of total testosterone.
Conclusion
Prevalence of decreased level of total testosterone among obese male patients with type 2 diabetes was found to be 52.7 %. Symptoms of androgen deficiency should be corroborated with testosterone level to establish a multidisciplinary approach for management of hypogonadism.

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P742

Correlation of different types of headaches, their severity with BMI and hyperandrogenism in PCOS patients

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Background
Polycystic ovary syndrome (PCOS) is a highly prevalent disorder affecting 4%-20% of reproductive-aged women worldwide. Those affected by PCOS have a variety of clinical findings, which can affect their quality of life. Evidence suggests that polycystic ovarian syndrome and migraines are linked. However, the relationship between polycystic ovary syndrome and other types of headaches and their severity has not been studied.
Objectives
The purpose of this study was to look into the prevalence and severity of different types of headaches in individuals diagnosed with PCOS, as well as how this could be influenced by BMI, hyperandrogenism, menstrual dysfunction, and other risk factors of PCOS.
Methods
A cross-sectional study was conducted on 473 females with the diagnosis of PCOS who were surveyed using an anonymous questionnaire that included questions about their age, medications, PCOS clinical symptoms, and menstrual cycle. Chi square test and odds ratio were preferred analysis methods for this study.
Results
466 (98.5%) of the 473 respondents experiencing headaches. Those with BMIs more than 30 had a higher incidence of headaches (Chi square $=9.613$; df$=9$; $P=0.3827$) and Females above the age of 25 have a greater number of different forms of headaches, (Chi square $=3.284$; df$=3$; $P=0.3499$), this was not shown to be statistically significant. The Chi square test for headache intensity in girls with PCOS with various BMI (underweight, normal, overweight, and obese) revealed that headaches were severe in females with BMI more than 30. (Chi square $=14.60$; df$=6$; $P=0.0236$) and headache intensity increased with BMI, especially during menstruation. Chi square $=22.62$; df$=6$; $P=0.0009$). OCPs do not influence the incidence of any kind of headache in females with PCOS. Metformin use was mildly associated with tension headaches (O $r=1.12$, $P=0.6107$, 95%CI-0.7489, 1.676) and cluster headaches (OR$=1.366$, $P=0.1155$, 95% CI-0.9282, 2.01). Oral contraceptive use was not associated with migraines in PCOS patients. (OR$=0.932$, $P=0.762$, 95% CI$=$ 0.6276, 1.384)
Conclusion
The results of the study reveal that tension and migraine headaches are the most prevalent types of headaches among PCOS patients. During menstruation, the pain rises in intensity. This brings up new opportunities for the development of preventative and management strategies for PCOS patients with frequent headaches, which effectively contribute to an increased quality of life.

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P743

Sertoli-leydig cell tumours

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Introduction
Sertoli-leydig cell tumours are neoplasms of ovarian sex cord stromal cells and account for 0.5-2% of ovarian tumours with reported incidence <0.5 % of all ovarian tumours. These tumours usually manifest in women at younger age (in 75 % patients average age of onset <30). Majority of these tumours produce hormones and up to 80% of ovarian Sertoli-Leydig cell tumours can manifest with signs of virilization.
Case report
18 year old female who presented to endocrine outpatients with secondary amenorrhoea of 6 months and raised androgens on biochemical testing. Further history revealed she had noticed change in voice for 6 months, increase in facial hair growth, reduction in breast size and enlargement of clitoris. Biochemical testing yielded high testosterone level of 8, raised FAI of 12.8, normal prolactin, HSE2 138, LH 19.4 and FSH 2.9. She had never used contraception and was not on any regular medication. Repeat hormone profile was booked from clinic along with U/S pelvis,17OH PG and DHEAS. On repeat testing testosterone levels had risen to 12.6 from 8, with FAI of 28.6, 17OH progesterone of 16.1 (0.5-4.4) and raised DHEAS of 11.1 (1.8-10). Right ovary showed multi septated ovarian cyst. Due to raised DHEAS and 17 OHPG adrenal MRI was requested and case was discussed with gynaecology. MRI adrenal was unremarkable. Patient attended A n E department with abdominal pain, repeat ultrasound and MRI pelvis was arranged which showed progressively enlarging multi cystic right ovary with increased complexity and moderate volume of pelvic fluid/ascites. She underwent laparotomy and tumour excised along with associated fallopian tube, histology examination of the mass confirmed tumour to be Sertoli-Leydig cell tumour. She is doing well at 6 months follow up with return of menstruation.
Discussion
Sertoli Leydig cell tumours are rare tumours of ovarian stromal sex cord origin. Due to low incidence of these tumours, their presentation to endocrine clinic is a rarer

occurrence. Majority of ovarian sex cord stromal tumours are hormonally active and some can present without typical symptoms of abdominal pain, it is important to recognise this early and consider this as part of differential diagnosis in females with signs of virilization. Early recognition and appropriate referral ensures optimal outcome

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P744

Parental Experience of the Announcement of the Diagnosis of Diabetes in Adolescents

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Introduction
The discovery of a chronic pathology in a child upsets the pre-existing family balance and generates emotional reactions in the family. With the incidence of type 1 diabetes doubling over the past 30 years, many families find themselves faced with this emblematic situation.
Objectives
To describe the parental experience of being diagnosed with type 1 diabetes in adolescents.
Materials and Methods
Retrospective descriptive study, carried out at the Endocrinology and Metabolic Diseases Department of Casablanca, during the year 2022, including 45 parents of adolescent type 1 diabetics followed in transition consultation, questioned about the experience of the announcement diabetes.
Results
The circumstances of the diagnosis were an inaugural ketosis in 43 cases, and only 2 cases of diabetic ketoacidosis, our patients were aged between 15 and 19 years. The testimony of the parents was collected on average 6 months after the diagnosis. The announcement was made to both parents in 32 cases and the mother alone in 8 cases. Fear of the future was reported in 34 parents, and shock in 30 parents, thus representing the most frequently cited affects, followed by anxiety in 24 parents, and guilt in 5 parents, including 2 diabetic parents. All the parents interviewed said they wanted an information and education program dedicated to parents.
Conclusions
The trauma caused by the announcement of diabetes, a chronic disease requiring a change in the lifestyle of the whole family justifies bringing the 2 parents together from the initial interview to inform them about diabetes and allay some of their fears as well as to educate them on acute complications at first and degenerative later.

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P745

Models of care for polycystic ovary syndrome: A systematic review

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Introduction
Polycystic ovary syndrome (PCOS) is associated with broad reproductive, metabolic and psychological complications, as well as significant heterogeneity in presentation between and within individuals across the lifespan. Therefore, there is a need for a multidisciplinary approach. A model of care (MoC) is conceptualised as an overarching provision of care that is codesigned with end-users and aligns with evidence-based practice and defined standards. The international PCOS guideline from 2018 recommends to ensure best practices while providing care for women and individuals with PCOS. Exploration of existing MoCs for PCOS can help identify and share learnings from current practice.
Aim
To perform a systematic review to identify available PCOS MoCs and describe their characteristics and alignment with the international PCOS guideline.
Methods
This systematic review was prospectively registered on PROSPERO CRD42022346539. OVID MEDLINE, All EBM, PsycInfo, EMBASE, and CINAHL were searched from inception until 11 July 2022. Any English study with a detailed description of a PCOS MoC was included. Abstracts, study protocols, and clinical trial registrations were excluded. Data extracted included the service name and detailed descriptions of the model, specialities involved, services provided in alignment with the PCOS guideline and evaluations. Data were synthesised narratively.
Results
Of 3670 articles, five articles describing four MoCs were included in our systematic review—two from Australia, three from the US, and none from developing countries. All MoCs described a multidisciplinary approach ranging from 4-8 specialties including a health nurse, dietitian, endocrinologist, gynaecologist, psychologist, dermatologist, etc. Two MoCs—Monash Health state-wide integrated PCOS service and the Multidisciplinary clinic for PCOS at Children's Hospital Colorado—described all aspects of PCOS care aligning with the international guideline. These include providing education on long-term risks, lifestyle interventions, screening and management of emotional well-being, cardiometabolic diseases, and dermatological and reproductive elements of PCOS. Two MoCs were evaluated via focused-group discussions, semi-structured interviews, and surveys to understand patients' and healthcare professionals' satisfaction, with generally positive findings. Only one MoC explored the impact of their service on patients' health outcomes and showed improvement in BMI and weight.
Conclusion
There is limited literature describing PCOS MoCs in routine practice. Future research should explore the various PCOS MoCs globally, particularly from low- and middle-income countries, and their alignment with international guidelines as well as focusing on patient satisfaction and needs. This may facilitate the exchange of best practices between institutions and support the development of a best-practice framework in PCOS care.

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P746

Falsely elevated estradiol levels in a young female with iatrogenic menopause

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False elevation of estradiol(E2) due to immunoassay interference is a rare but important phenomenon reported in the literature. It is most commonly related to cross-reactivity(CR) from drugs sharing structural similarity with E2, namely fulvestrant and exemestane. These laboratory interferences(LI) can lead to unnecessary investigation/inappropriate treatments. Therefore, in such instances, a more selective and sensitive method is required. We present the case of a young female with high E2 levels inconsistent with her clinical iatrogenic menopause. A 34 years-old female with a history of breast cancer(BC) was examined for estradiol(E2) concentration. Her past medical history was remarkable for BC diagnosed at age 31. She underwent a right simple mastectomy with sentinel node biopsy. Pathology revealed an invasive BC, that was estrogen and progesterone receptor positive-pT4N0M0. Oocyte cryopreservation was performed. The patient was treated with chemotherapy(doxorubicin, cyclophosphamide, paclitaxel), followed by locoregional radiotherapy. Given her high-risk lifetime BC occurrence as well as the fact that her BC was strongly estrogen receptor positive, she initiated ovarian suppression with goserelin plus exemestane. The determination of serum E2 concentration, being a part of the patient's therapeutic monitoring, was requested. E2 levels were persistently elevated(90-100pg/ml) over a year, measured by the chemiluminescent immunoassay method, that rendered exemestante therapy ineffective. The patient had a complete clinical response to treatment, according to clinical symptoms, radiologic findings and normal levels of tumor biomarker. One year after starting hormone therapy(HT), since she maintained elevated levels of E2, a bilateral salpingo-oophorectomy was performed, no pathological changes were found. Three months after surgery she was referred to our Endocrinology Department for further investigation due to persisting elevated E2 levels (83-87). She was in amenorrhea since chemotherapy, reporting vasomotor symptoms since that time. Her clinical status was inconsistent with elevated E2 values.

A suspicion of LI was raised. To rule out the suspected exemestane CR with 17β-estradiol levels were subsequently obtained and tested with a more sensitive and specific method(access sensitive estradiol-assay-competitive binding immunoenzymatic assay-Beckman Coulter), which showed the patient's serum estradiol levels were undetectable. This confirmed that an exogenous compound, most likely exemestane, caused the CR with the immunoassay resulting in falsely increased serum E2. Clinicians should keep in mind that LI must be considered in the presence of increased estradiol levels that are contradictory to the clinical picture, in a patient under anti-HT, and therefore should be confirmed using alternative assays.

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P747

Post-Menopausal Hyperandrogenism Secondary to an Ovarian Cause – When Surgery is not An Option

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Introduction
Hyperandrogenism is a relatively common medical condition, however severe post-menopausal hyperandrogenism should raise suspicion of a malignant etiology and prompt clinical evaluation. Furthermore, androgen excess has also been associated with severely decreased quality of life. As such, identification of its cause and adequate treatment should not be delayed.
Case Report
We report a case of a 66-year-old woman, who had a 5-year history of worsening hirsutism - particularly on the face, neck, chest, back, and abdomen (Ferriman-Gallwey score = 15) – without signs of virilization. She had been taking prednisolone 5 mg for the last 7 years due to hemolytic anemia. She also had a prior medical history of diabetes, hypercholesterolemia and hysterectomy with right oophorectomy. On examination she had central obesity, with a BMI of 38 Kg/m2, facial plethora and buffalo-hump, and male pattern hair loss. Laboratory tests showed a total testosterone of 253 ng/dl (2.9-40.8), delta-4-androstenedione 1.7 ng/ml (0.3-3.3), dehydroepiandrosterone sulfate 16.3 (9.4-246), follicular stimulating hormone (FSH) 48.1 IU/l, luteinizing hormone (LH) 30.1 IU/l and a serum estradiol 45.0 pg/ml. A CT scan of the abdomen did not show adrenal lesions. Transvaginal pelvic ultrasound did not identify the left ovary, hence a pelvic MRI was performed which showed a solid mass with 18mm in the left ovary. A GnRH stimulation test was performed - one month following the administration of triptorelin (3 mg) total testosterone levels decreased to 25 ng/dl, LH to 0.87 IU/l and FSH to 6.03 IU/l. Given the previous surgical history and medical comorbidities with a significantly increased operatory risk, the surgical team decided against surgery and the patient was initiated on oral anti-androgenic medication - cyproterone 50 mg daily. Two months after starting therapy there was a remarkable clinical improvement, with significant regression of alopecia and decrease of the terminal hair on the chest, back and abdomen. A biochemical response was also achieved, with total testosterone levels decreasing to 33 ng/dl. No side effects were reported.
Conclusions
A detailed clinical history, physical examination and directed laboratory and imaging exams are essential to identify the cause of post-menopausal hyperandrogenism. Treatment should be promptly started, ideally aimed at the primary cause. However, especially in case of benign etiologies and/or unacceptable surgical risk, anti-androgenic medications can be an alternative. This case illustrates that when surgery is not feasible, hyperandrogenism control is still achievable using anti-androgenic therapy.

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P748

Small for gestationnal age and short stature: What is the growth prognosis?

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Introduction
The term « Small for gestationnel age » (SGA) defines newborn infants whose birth weight and/or crown-heel length is less than 10th percentile for gestational age, or at least 2 standard deviation below the mean for the infant's gestational age. It is considerd as a common aetiology of short stature. The aim of our study is to describe the prevalence of SGA in short stature, and thee growth prognosis in this population.
Material and methods
We conducted a retrospective study on 14 patients presenting with short stature and SGA admitted in the Endocrinology-Diabetology-Nutrition department of Mohammed-VI University Hospital Center of Oujda, in the eastern of Morocco. The results were collected and processed using the SPSS software V21.
Results
The prevalence of patients defined as SGA among patients presenting with short stature was 7%. The mean age of patients at diagnosis was 8 years ± 4, and the sex ratio M/F was 1,8. The mean birth weight of patients was 2,2 ±0,4 kg. No obstetric history was found in any patient's mother, and a neonatal suffering history was found in 25% of patients. The mean height at diagnosis was 120 cm ±18 cm, and the mean weight was 22 kg ±7. The mean standard deviation (SD) score for height was -4 SD ±0,8, and the mean standard deviation score for weight was -2,8 ±0,7SD. The median difference between bone age and chronological age was 16 months (ranging from 10 to 49 months). A Glucagon-Propranolol test was performed in 75% of patients. One patient had a partial growth hormone deficiency, in whom a Silver syndrome was suspected. Growth hormone (GH) therapy was assessed in 78,5% of patients. It was not used in 21,5% of patients for lack of means. After one year of treatment, the mean height of patients was 131 cm ±21 cm, with a gain of 11 cm, and the mean standard deviation (SD) score for height was -3,6SD ±1SD.
Discussion and conclusion
An increased risk for short stature is discribed in infants born small for gestationnal age. Growth hormone therapy is indicated in children born small for gestationnal age with failure to catch up to the normal height percentiles. The growth promoting effect of continuous GH treatment was noticed in our case series.

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Thyroid

P206

Thyroid Pyramidal Lobe Detection by Ultrasound in 1275 Consecutive Patients

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Background
The thyroid pyramidal lobe (TPL) represents a normal anatomical variation of the thyroid gland. Intraoperative TPL identification is of paramount significance, taking into account that the remnant TPL leads to higher thyroglobulin, could contain thyroid carcinoma foci and lead to recurrence.
Methods
We conducted a prospective single-center, single-operator study to identify TPL in 1275 consecutive patients undergoing thyroid ultrasound for any indication. We extended the standard technique to actively search for TPL. The findings reported were presence and site of the TPL, presence of incidentally discovered nodules in TPL and thyroglossal duct cysts (TGDC). We excluded patients who underwent thyroid surgery or radioiodine therapy.
Results
Of the 1275 consecutive patients (1011 female), TPL was identified in 584 (45.8%), 12 (0.9%) had TGDC, 2 had hemiagenesis of the left thyroid lobe, 1 had thyroid agenesis with ectopic thyroid tissue. 227 patients (38.9%) presented with left-sided TPL, 220 (37.7%) with right-sided, 111 (19%) with median line and 26 (4.5%) with bilateral TPL. In 27 patients (4.6%), we identified incidental asymptomatic nodular lesions or possibly pseudonodular lesions (in some cases probably structural heterogeneity due to autoimmune thyroid disease) within TPL.
Conclusions
We suggest to routinely screen for thyroglossal duct remnants (TPL or TGDC) during thyroid ultrasound. This may reduce the rate of postoperative remnant TPL, obtain lower postoperative thyroglobulin levels and potentially lead to less frequent radioiodine therapy indication. Incidental discovery of thyroid nodules within TPL could also play important role in patient management. The investigation is not time-consuming (average time <10 seconds) and could be considered a cost-effective strategy.

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P207

Thymic Hyperplasia and Graves's Disease: A Non-Incidental Association

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Introduction
Grave's disease (GD) is an autoimmune disease characterized by the development of thyroid-stimulating hormone (TSH) receptor antibodies that have a stimulating effect on the thyroid gland. There is a rare but non-incidental and well-documented association between GD and thymic hyperplasia (TH). Nonetheless, this association is often underdiagnosed in routine clinical practice and the mechanisms behind this association have yet to be thoroughly elucidated. Thymic regression with the resolution of hyperthyroidism is characteristic. We describe one case of TH in a patient with Grave's disease.
Case Presentation
We present the case of a 40-year-old male with no personal or family history of interest, referred for primary hyperthyroidism. A chest computed tomography (CT) scan had been performed in Primary Care in the setting of constitutional symptoms, and revealed a 3 cm anterosuperior mediastinal mass consistent with TH. No signs or symptoms of myasthenia gravis were noted. A positron emission tomography CT scan was performed in order to exclude a thymoma, revealing no metabolic activity increase. He presented with diffuse goiter, hand tremor and increased heart rate. Laboratory findings showed TSH <0.01 mIU/l [0.380-5.330] with T4L 4.2 ng/dl [0.54-1.24]and positive anti-TSH receptor antibodies (TRAB)(40 U/l, reference range <1.75). Thyroid ultrasound showed an enlarged thyroid with increased vascularity. Based on these findings, the patient was diagnosed with GD and coexisting TH. Since TH is an uncommon but known manifestation of GD, no further investigations of the thymic mass were done and medical treatment of GD was started with a titration regimen of methimazole and propranolol. A conservative and observational approach was taken to monitor TH. Twelve months later and after maintaining a euthyroid state with negative TRAB, a repeat CT scan was performed and revealed total regression of the mass seen on the previous CT.
Conclusion
Mediastinal tumours located in the anterosuperior mediastinal compartment are usually malignant, the detection of an anterior mediastinal mass usually leading to biopsy or even surgical removal. Nonetheless, in Grave's disease the diagnostic approach is different. Resolution of hyperthyroidism together with back to normal anti-TSH receptor antibodies is associated with regression of thymic hyperplasia. Several hypotheses have been proposed to explain the mechanisms behind the association of GD and TH, including an immunology-based pathogenesis and a direct thymic trophic effect from excess thyroid hormones. Benign evolution as evidenced by regression of thymic hyperplasia after resolution of hyperthyroidism in all cases described in the literature, supports a conservative approach.

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P208

Novel Thyroid Hormone Receptor-β Agonist TG68: a polypharmacological approach for the treatment of obesity-associated diseases

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Obesity is a multifactorial disease in which environmental conditions and genetic factors play an important pathogenic role [1]. Interestingly, some of these obesogenic environmental and genetic conditions are shared with neurodegenerative diseases (NDD). The common biological mechanisms involved in obesity and NDD are insulin resistance, pro-inflammatory cytokines, and oxidative damage, in turn leading to cognitive dysfunction or cell death. In this aspect, a poly-pharmacological drug approach which targets multiple pathological pathways at the same time, should provide the best way to treat such complex networked diseases. Activation of thyroid hormone receptor β (THRβ) has shown beneficial effects on metabolic and neurologic alterations, without cardiotoxicity. Therefore, selective TRβ-agonists might represent promising multitarget agents for the treatment of interlinked diseases such as obesity and NDD. Recent investigations, allowed the selection of the novel thyromimetic TG68 as a very powerful lipid lowering, transthyretin (TTR) protein stabilizer, and antiamyloid agent [2,3]. With the aim to expand our knowledge on the multitarget potential of this novel TH analog, we investigated the effects on lipid metabolism, neuroinflammation and behavior produced by chronic administration of TG68 in high fat diet (HFD) obese and insulin resistant mice, a well established model of obesity/neuroinflammation neurotoxicity. Even though still at a preliminary level, the results of our study provided evidence that in HFD mice (24 CD-1 male mice exposed to HFD C1090-60 for 10 weeks), treatment with TG68 (10 mg/kg/day; 7days; in drinking water) significantly ($P=0.02$) reduced anxiety, as detected by performing stretch-attend posture (SAP) tests, while inducing a 20% body weight loss and a significant ($P<0.05$) decrease in blood lipid levels, including cholesterol and triglicerides. A significant ($P<0.01$) anti-inflammatory activity in LPS/THFa stimulated human microglial cells (HMC3) was also observed after treatment with 10 μM TG68, providing support to the ability of this novel THRβ-selective thyromimetic to efficiently modulate multiple pathological pathways involved in complex networked diseases, such as obesity and NDD.
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P209

The TNAPP web-based algorithm improves thyroid nodule management in clinical practice. A retrospective validation study

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The detection of thyroid nodules has been increasing over time, resulting in an extensive use of fine-needle aspiration (FNA) and cytology. Tailored methods are required to improve the management of thyroid nodules, including algorithms and web-based tools. To assess the performance of the Thyroid Nodule App (TNAPP), a web-based, interactive algorithmic tool, in improving the management of thyroid nodules, we carried out a preliminary analysis on a cohort of outpatients. One hundred twelve consecutive individuals with 188 thyroid nodules who underwent FNA from January to December 2016 and thyroid surgery were retrospectively evaluated. Neck ultrasound images were collected from a registry and re-examined to extract data to run TNAPP. Each nodule was evaluated for ultrasonographic risk and suitability for FNA. The sensitivity, specificity, positive and negative predictive values, and overall accuracy of TNAPP were calculated and compared to the diagnostic performance of two algorithms by the American Association of Clinical Endocrinology/American College of Endocrinology/Associazione Medici Endocrinologi (AACE/ACE/AME), and the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS). TNAPP performed better in terms of sensitivity (>80%) and negative predictive value (68%) with an overall accuracy of 50.5%, which was similar to that found with the AACE/ACE/AME algorithm. TNAPP displayed a slightly better performance than AACE/ACE/AME and ACR TI-RADS algorithms in selectively discriminating unnecessary FNA for nodules with benign cytology (Bethesda class II: TNAPP 32% vs. AACE/ACE/AME 31% vs. ACR TI-RADS 29%). The TNAPP reduced the number of missed diagnoses of thyroid nodules with suspicious and highly suspicious cytology (Bethesda classes V + VI: TNAPP 18% vs. AACE/ACE/AME 26% vs. ACR TI-RADS 20.5%). A total of 14 nodules that would not have been aspirated were malignant, 13 of which were microcarcinomas (92.8%). TNAPP's use of size >20 mm as an independent determinant for considering or recommending FNA reduced its specificity. The rate of malignant nodules missed because of inaccurate characterization at baseline by TNAPP was lower compared to the other two algorithms and the tumors were microcarcinomas, suggesting the risk of missing diagnoses would have been favorable in terms of overall patients' prognosis. Overall, the TNAPP algorithm is a reliable, easy-to-learn tool that can be readily employed to improve the selection of thyroid nodules requiring cytological characterization. Additional studies are needed to confirm and guide the development of future iterations that incorporate different risk stratification systems and targets for diagnosing malignancy while reducing unnecessary FNA procedures.

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P210

The role of 18F-DOPA-PET/CT in medullary thyroid cancer patients with biochemical incomplete response

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Background
PET/CT scan with ^{18}F-fluoro-dihydroxyphenylalanine (^{18}F–DOPA) is an emerging useful tool in medullary thyroid cancer (MTC) patients with high calcitonin (CTN) values. The aim of this study is to evaluate the potential usefulness of ^{18}F-DOPA-PET/CT in MTC patients with biochemical incomplete response (BiR) (detectable CTN values and negative/indeterminate findings at CT scan with i.v. contrast).
Materials and Methods
Fifty-three MTC patients with BiR performed ^{18}F-DOPA-PET/CT scan between May 2021 and December 2022 after having performed CT scan with i.v. contrast.
Results
Most of patients were females (60.4%). The median age at the diagnosis was 47 years. Sixteen (30.2%) patients were positive for RET germline mutation. At the time of ^{18}F-DOPA-PET/CT [median 37 months (IQR: 102-196.5) from diagnosis], the median serum CTN value was 399 (165-1135) pg/ml. ^{18}F-DOPA-PET/CT was negative in 15 (28.3%) cases, while an uptake of the radiotracer was detected in 38 (71.7%). Conversely, CT scan was negative in 21 (39.6%) while in the remaining 32 (60.4%) patients, indeterminate findings were highlighted. When comparing the two imaging methods, both were negative in 11 (20.8%) cases. In the remaining 10 (18.9%) cases of negative CT scan; ^{18}F-DOPA-PET/CT showed pathologic uptake mainly in neck. However, in 2 patients the uptake was in liver. Among 32 patients with indeterminate findings at CT scan, 28 showed an uptake at ^{18}F-DOPA-PET/CT while 4 did not. When we analyzed the concordance between the two methods (uptake of ^{18}F-DOPA in the same sites of indeterminate lesions described at CT scan), 9 patients showed a concordance while 4 patients a discordance (uptake of ^{18}F-DOPA in other sites than those described at CT scan). The other 15 patients showed a partial concordance, most of whom (9/15 – 60%) had more indeterminate lesions at CT scan than ^{18}F-DOPA uptake.
Conclusions
In most of the cases of MTC patients with BiR and negative or indeterminate findings at CT scan; ^{18}F-DOPA-PET/CT scan showed radiotracer-enhancing lesions. Therefore, in this setting; ^{18}F-DOPA-PET/CT can be useful to clarify and define as metastases those lesions with indeterminate features at CT scan. However, although these findings are relevant and useful to better follow-up the disease, the clinical management rarely has been changed.

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P211

Improving the surgical indication of the Indeterminate TIR3B nodules: a prediction model based on clinical, ultrasound and cytological features

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Introduction
Indeterminate cytology still puzzles clinicians, due to its wide range of oncological risks. The new Italian cytological classification introduced in 2014 by SIAPEC-IAP split this category into TIR3A and TIR3B, according to a different cancer risk of $<10\%$ and $<30\%$, respectively. Consequently, TIR3B nodules still have a surgical indication, even if more than half of cases will not result in thyroid cancer. The present study aims to analyse a consecutive series of TIR3B nodules referred to surgery, to identify potential features able to improve the surgical indication.
Methods
A consecutive series of thyroid nodules referred to the Endocrine Unit of Careggi Hospital from 1st May 2014 to 31st December 2021 has been considered to build a prediction algorithm. The main clinical, US and cytological features have been collected, with particular regard to the secondary cytological features such as cell configurations, presence of colloid, aggregates, anisonucleosis, nuclear atypia and Hurtle cells. According to Akaike Information Criterion (AIC), a stepwise logistic regression has been performed to find the best prediction algorithm, using the histological outcome as the dependent variable. Thereafter, this algorithm has been verified in a smaller confirmatory sample of consecutive TIR3B diagnosed and referred to surgery from 1st January 2022 to 31st June 2022.
Results
Of 502 TIR3B nodules referred to surgery, 451 cases were included in the exploratory analysis. The observed rate of positive histology was higher than expected, with 161 cases (36%) of thyroid cancer ($P=0.010$). Considering the final outcome, a stepwise logistic regression showed that the presence of colloid (OR = 0.18, CI95%:0.04-0.88, $P=0.034$), age>55 years (OR = 0.49, CI95%:0.31-0.77, $P=0.002$) and a nodule size >18 mm (OR = 0.354, CI95%:0.22-0.56, $P<0.0001$) were favourable prognostic factors, at odds with the presence of chronic autoimmune thyroiditis (OR = 1.7, CI95%:1.05-2.9, $P=0.032$), Hurtle Cells (OR = 4.2, CI95%:1.35-14.1, $P=0.020$), hypoechoic nodules (OR = 2.79, CI95%:1.62-4.81, $P=0.0002$), aggregate cells disposition (OR = 4.55, CI95%:1.57-13.2, $P=0.005$), and anisonucleosis (OR = 5.15, CI95%:1.6-166.1, $P=0.0049$). A unified prediction algorithm was built according to the multivariate results. A score >14.5 showed a sensitivity of 60.1% and a specificity of 76.8% in predicting the unfavourable outcome (AUC = 0.748, 95CI:0.699-0.797, $P<0.0001$), which corresponded to an OR = 4.98 (95CI:3.24-7.65, $P<0.0001$). When applying the same algorithm on a confirmatory sample of 58 TIR3B cytology, a threshold of 14.5 points showed a positive and a negative predictive value of 53% and 80%, respectively.
Conclusions
A new predictive algorithm which considers the main clinical, US and cytological features can significantly improve the oncological stratification of TIR3B cytology.

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Iodine supply and thyroid status of women with gestational diabetes mellitus and their impact on birth outcomes

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Introduction
Urinary iodine concentration (UIC) and neonatal thyroid stimulating hormone (neoTSH) concentrations can reflect changes in iodine status and serve as a sensitive marker of iodine intake in pregnancy. As gestational diabetes mellitus (GDM) requires some diet modification, the study aimed to map the situation of iodine intake in women with GDM compared to healthy pregnant women and explore a relationship to thyroid function.
Methods
In the two groups consisting of 195 pregnant women with GDM and 88 healthy pregnant women, we assessed UIC using spectrophotometry after alkalisation and demineralisation and serum concentrations of TSH, free thyroxine (FT4) and autoantibodies against thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) were detected by chemiluminescent immunoassay. Neonatal TSH was determined in the newborns of women with GDM by immunofluorescence from a dry drop of blood on a screening card.
Results
The median of UIC was significantly lower in women with GDM than in the control group (89.50 mg/l vs 150.05 mg/l; $P<0,001$). The optimal iodine supply was found only in nine women with GDM (4.62%) and 33 healthy pregnant women (37.5%) ($P<0.001$). Most pregnant women with GDM (88.72%) and half of the controls (50.00%) had iodine deficiency ($P<0.001$). Neither TSH serum concentrations nor the prevalence of TSH >4 IU/l were different in both groups. However, the women with GDM had a significantly higher prevalence of isolated hypothyroxinemia compared to controls (12.31 % vs 3.41 %, $P=0.032$). Also, the prevalence of neonatal TSH >5 IU/l was 5.22% in newborns of women with GDM and signalled iodine deficiency. The positive association between FT4 and HbA1c in women with GDM was found in the regression model. Hypothyroxinemia <11.5 pmol/l was also associated with a higher risk of preterm birth in the same group.

Conclusion
UIC was lower in women with GDM than in control and corresponded with the iodine deficiency. Most pregnant women with GDM (88.72%) and half of the controls (50.00%) had iodine deficiency. In addition, the women with GDM had a significantly higher prevalence of isolated hypothyroxinemia compared to controls (12.31 % vs 3.41 %, $P=0.032$). Also, the prevalence of neonatal TSH $>$ 5 IU/l was 5.22% in newborns of women with GDM and signalled iodine deficiency.

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P213

Patients with Covid-19 induced atypical thyroiditis have thyroid-resident memory T-cells specific for SARS-CoV-2

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Background
The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic disease (Covid-19) is associated with the onset of thyroid dysfunction via multiple mechanisms. Patients hospitalised for severe Covid-19 disease may develop painless atypical thyroiditis coexisting with non-thyroidal illness syndrome, which determines transient thyrotoxicosis with quick restoration of euthyroidism during the following weeks. However signs of thyroiditis at ultrasound and scintigraphy scans may persist up to one year. The SARS-CoV-2 immune responses play a key role in inducing secondary thyroid dysfunction, but little is known about anti-viral immune responses in the thyroid gland.
Methods
We analysed T-cell responses in 7 patients with severe Covid-19 disease developing atypical thyroiditis (COV-A-SAT). Paired blood and ultrasound-guided thyroid fine-needle aspiration (US-FNA) samples were obtained after 4 and 8 months following SARS-CoV-2 infection. Extracted lymphocytes were immunophenotyped by flow cytometry and stimulated with SARS-CoV-2 peptides. HLA-matched MHC I and II dextramers specific for SARS-CoV-2 peptides were also used to identify SARS-CoV-2-specific T-cells. The presence of intra-thyroid SARS-CoV-2 RNA on thyroid US-FNA samples was tested by real-time reverse transcriptase polymerase chain reaction 4 months post-infection.
Results
No intra-thyroid SARS-CoV-2 RNA was found 4 months post-infection. Despite the apparent viral clearing, COV-A-SAT patients still showed increased systemic T-cell activation as well as cytotoxic and Th1 effector cells, which returned to normal levels 8 months post-infection. Moreover, anti-SARS-COV2-specific CD4+ and CD8+ T-cell responses were readily detectable in peripheral blood 4 months post-infection, but were hardly detectable after 8 months. Unbiased bioinformatic analysis of T-cells in the thyroid gland and in peripheral blood unveiled unique T-cell clusters, in particular CD103+CD69+ tissue-resident memory cells (TRM) in the thyroid, and identified CXCR3+T-cells as their putative precursors in the blood. Importantly, SARS-COV2-specific T-cells were enriched in the thyroid gland, and acquired a TRM phenotype in particular 8 months post-infection.
Conclusions
These findings suggest that atypical thyroiditis developed by patients with severe Covid-19 is characterised by a prolonged, yet largely transient, systemic anti-viral effector T-cell response that results in the generation of long-lived tissue-resident memory cells in the thyroid. This local immune response may in part explain the persistence of signs of thyroiditis at thyroid ultrasound and scintigraphy scans up to one year following infection, despite the presence of normal thyroid function. Long-term clinical consequences are unknown.

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Depression among hyperthyroid patients and the impact of Graves' orbitopathy

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Background
Thyroid hormones have regulatory effect on serotonin and noradrenaline and thyroid dysfunction is closely linked to some mental disorders. Besides depression and anxiety, and increased risk for suicide is demonstrated in patients with Graves' disease (GD).
The aim
of our research was to determine the symptomatology of depression in patients with hyperthyroidism and Graves' orbitopathy (GO) and compare it with hyperthyroid patients without GO. We also studied the influence of GO as an additional stressful long-lasting disease, known to have a great impact on quality of life due to disfiguring and eye function reduction.
Material and method
The study group included 36 patients (10 males and 26 females; age range 33-72 years) with GO, and 20 patients (3 males and 17 females; age range 21-75 years) without GO. For the assessment of depressive symptoms, we used the 9-item Patient Health Questionnaire (PHQ-9) for all patients and a disease-specific GO-QOL questionnaire for 30 patients with GO. The total scores for both GO-QOL scales (visual functioning and appearance score) were 0-100%, the higher values, the better quality of life. The results do not represent a definitive diagnosis of depression. All subjects were euthyroid on thioamides. Patients with GO had active moderately severe disease.
Results
In the group with GO, 5.6% had minimal symptoms of depression, 44.4% mild, and 50% had moderate-to-severe symptoms of depression. In the group without GO, 35% of patients had no symptoms, 35% had minimal symptoms, 25% had mild, and 5% moderate symptoms of depression. The frequency of depressive symptoms was significantly higher in patients with GO than in the control group ($P=<0.001$). The majority of the patients (38.8%) had difficulty concentrating when doing things like reading newspapers or watching television. In the GO-QOL questionnaire, minimal changes in the visual functioning were found in 30% of GO patients, while 33.3% had moderate, and 36.6% severe changes in visual functioning. The appearance score showed that 43.3 % of patients thought to have minimal, 46.6 % moderate, and 10 % severe changes in appearance.
Conclusions
Hyperthyroidism may have a significant impact on the development of depressive symptoms (low mood and difficulty enjoying things, loss of appetite, disturbed sleep, etc.). Furthermore, our results indicate that patients with GO are at greater risk of experiencing depressive symptoms. Thus, psychotherapy should be included in the treatment of hyperthyroid patients, particularly in those with Graves' orbitopathy.

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P215

Nonfunctioning thyroid nodules in graves' disease – do they harbor a higher risk of malignancy?

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Introduction
The prevalence of palpable thyroid nodules in Graves' disease (GD) is approximately 15%. Cytopathologic interpretation in GD is challenging due to frequent cytomorphologic changes, namely after radioactive iodine (RAI) therapy. Some of the few published studies regarding fine-needle aspiration (FNA) in patients with GD, suggest an increased risk of malignancy of thyroid nodules arising in GD patients. However, the results are inconsistent, and there is no consensus.
Objective
To characterize FNA results of thyroid nodules in GD patients and analyze if there is a higher rate of malignancy.
Methods
We conducted a retrospective review that included all patients who underwent FNA between 01/09/2021 and 01/09/2022 at our center. Statistical analysis was done using SPSS Statistics v.29.0. A P-value <0.05 was considered statistically significant.
Results
We analyzed 1281 FNA results from 1015 patients with an average age of 61.76±12.12 years. There were 852 women (83.9%) and 163 men (16.1%). FNA results were nondiagnostic (ND) in 480 cases (37.5%), benign in 660 (51.5%), follicular lesion of undetermined significance (FLUS) in 102 (8.0%), follicular neoplasm (FN) in 13 (1.0%), suspicious for malignancy (SM) in 9 (0.7%) and malignant in 17 (1.3%). Thirteen patients included (1.3%) had GD and their cytopathological results were: ND in 7 (41.2%), benign in 7 (41.2%), FLUS in 2

(11.8%) and malignant in 1 (5.9%). None of the nodules in patients with GD was diagnosed as SM or FN. The patient with a malignant result underwent total thyroidectomy, and histological examination revealed papillary carcinoma. One of the patients with FLUS underwent total thyroidectomy, and histological examination was benign. One of the patients with GD had FNA done after RAI, and the result was ND. We found no significant difference between FNA results in patients with or without GD ($P=0.393$). In a subanalysis of patients with only benign or malignant cytological diagnosis, there was no significant difference in the rate of malignancy between patients with or without GD (12,5 *vs*. 2,4%, $P=0,19$).
Conclusion
In this study, there was no significant difference in the malignancy rate of thyroid nodules in patients with or without GD. These findings are inconsistent with some published studies suggesting that GD is associated with a higher risk of thyroid cancer. However, this study is limited by the small number of GD patients with thyroid nodules requiring FNA. This reinforces the need for robust studies to clarify the risk of thyroid malignancy in GD.

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UPLC-Q-TOF/MS-based metabolomics explored the metabolic mechanisms of thyroid cancer in different background

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Thyroid papillary carcinoma (PTC) is the most common endocrine tumor, Hashimoto's thyroiditis (HT) is considered to be closely related to PTC pathogenesis, but their relationship still needs verification and exploration. *Aim of the study*. To analyze the differences and similarities of the metabolic mechanism of thyroid papillary carcinoma in normal and HT background, and to explore the relationship between HT and PTC. The Ultra performance liquid chromatography-quadrupole-time of flight-mass spectrometry (UPLC-Q-TOF/MS) technology was used to analyze 61 PTC patient tissues (31 HT background and 30 normal tissue (NC) background). Potential biomarkers were screened from principal component analysis (PCA) to orthogonal partial least square (OPLS) discriminant analysis and further evaluated by ROC analysis. The HMDB was searched to identify potential differential metabolites and the final metabolic pathway analysis was performed by MetaboAnalyst 5.0. The HT and NC group had common metabolic pathways, such as taurine and hypo-taurine metabolism, arginine biosynthesis, alanine, aspartate and glutamate metabolism, arginine and proline metabolism and D-glutamine and D-glutamate metabolism. Furthermore, arginine, glutamic acid, cysteine, citric acid, malic acid, uracil and taurine showed statistical significance in PTC diagnosis (the area under the curve values of HT group and NC group were 0.867 and 0.973 respectively). The HT group had specific metabolic pathways, including aminoacyl-tRNA biosynthesis, glycine, serine and threonine metabolism. The metabolic profiles of the NC and HT groups had important similarities and differences in thyroid cancer. The correlation of PTC with HT may be related to aminoacyl-tRNA biosynthesis, serine and threonine metabolism.

Keywords:
Metabolomics; Hashimoto's thyroiditis (HT); Papillary thyroid cancer (PTC); Metabolism pathway; Biomarkers

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P217

Autoimmune thyroid disease: a risk factor for thyroid cancer?

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Introduction
Some studies suggest a possible link between autoimmune thyroid disease (AITD) and thyroid cancer (TC). However, existing data is inconsistent, and no consensus exists regarding this question.
Objective
The aim of this study was to analyze the association between TC and AITD, namely Hashimoto's thyroiditis (HT) and Graves' disease (GD).
Methods
We conducted a retrospective and observational study of all patients who underwent thyroid surgery (lobectomy or total thyroidectomy) between January 2020 and September 2022 at our center. Patients were diagnosed with AITD if they had at least one positive thyroid antibody (TPOAb, TgAb and/or TRABs) or if they had lymphocytic thyroiditis on histology. Statistical analysis was done using SPSS Statistics v.29.0. A P-value <0.05 was considered as statistically significant.
Results
We analyzed a total of 695 patients. 145 patients were excluded due to lack of data regarding the diagnosis of AITD. The 12 patients diagnosed with Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP) were also excluded. The average age at the time of surgery of the 538 patients included was 55.8 $\pm$ 15.1 years. There were 456 women (84.8%) and 82 men (15.2%). Most patients did not have AITD (61.0% *vs*. 39.0%) and had a benign histology (66.9% *vs*. 33.1%). We identified 171 patients (31.8%) with HT and 39 patients (7.2%) with GD. We found no statistically significant difference between the prevalence of TC in patients with or without AITD (33.8% *vs*. 32.6%; $P=0.393$). Also, no statistically significant difference was found in terms of occurrence of TC in a subanalysis of subjects with HT *vs*. subjects without AITD (38.6% *vs*. 32.6%; $P=0.18$). In the subgroup of patients with GD, there was a significantly lower percentage of malignancy than in patients without AITD (12.8% *vs*. 32.6%; $P=0.01$).
Conclusion
In this study, there was no positive correlation between the presence of AITD and the occurrence of malignant disease, contrary to what is suggested in some studies published in the literature. On the other hand, the malignancy rate was significantly lower in patients with GD compared to patients without thyroid AITD; this association may be due to the fact that, in most cases, the surgical indication in patients with GD is the treatment of hyperthyroidism and not the presence of a suspicious nodule. This reinforces the need for robust studies to clarify the possible role of thyroid autoimmunity in thyroid carcinogenesis.

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Sonographic pattern and risk factors and malignancy in indeterminate thyroid nodules

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Introduction
Fine-needle biopsy with cytologic evaluation remains the diagnostic test of choice to distinguish benign from malignant thyroid nodules, but fails to classify thyroid nodules in 15% to 30% of cases (indeterminate thyroid nodules-ITN). 'Rule out' molecular testing improves the diagnostic accuracy, with high sensitivity and negative predictive value, ranging from 86 to 96%. However, these tests are not widely available, and notably increase costs.
Objective
To determine if sonographic patterns of the nodule and risk factors of thyroid cancer are as useful as molecular testing.
Methods
We evaluate sonographic patterns and clinical characteristics of ITN with histologic diagnosis. We define EUTIRADS 2 and 3 as low risk (LR), EUTIRADS 4 as moderate risk (MR) and EUTIRADS 5 as high risk (HR). Sociodemographic variables and thyroid cancer risk factors (cervical radiotherapy, familiar history or PET-positive) were collected, and we calculate sensitivity (S), specificity (E), positive predictive value (PPV) and negative predictive value (NPV) for globally low risk patients (sonographic and clinical). Statistical study was carried out using SPSS v21
Results
From 2017 to 2021, 112 ITN with histologic diagnosis were included, 80.2% women, mean age 55.03 $\pm$15.5. 11.7% has at least one thyroid cancer risk factors. 29.7% had LR sonographic pattern, 40.5% MR and 29.7% HR. Nodule mean size was 30.2 mm $\pm$ 18 The overall malignancy rate was 24.4%. For LR ultrasound and no risk factors (28.5% of all patients) overall S, E, PPV and NPV were 97.1, 40.8, 43.03 and 96.8 respectively.

Conclusions
Sonographic patterns and thyroid cancer risk factors has as high NPV as a 'rule out' molecular test, and it should be a first step prior to consider it use.

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Graves ophthalmopathy in HIV patient: a case report

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Background
Graves disease is a resurgent autoimmune condition that is known to occur during treatment and immune reconstitution in HIV, and it is one of the commonly diagnosed endocrinopathies in these patients. Graves orbitopathy, on the other hand, is a situation that occurs less frequently. We report the clinical features and manifestations of thyroid-associated orbitopathy in a case of an HIV patient with Graves disease.
Case Presentation
A 48-year-old woman presented with spontaneous retrobulbar pain, exophthalmos, periodic diplopia, palpebral edema, and conjunctival hyperemia. The symptoms reported appeared and advanced during the previous 12 months. Anamnesis revealed that she was diagnosed with Graves disease 3 years ago and is on antithyroid medication and beta-blockers with moderate success in achieving euthyroidism. The patient is also receiving antiretroviral treatment for the last 5 years, as she was diagnosed with HIV 10 years ago. The patient is a chronic tobacco user, for about 30 years. On admission, the patient had freeT4 - 35,3 pmol/l, freeT3 - 12,0 pmol/l, and antithyroid medication was adjusted to obtain euthyroidism. On the clinical examination, we appreciated a CAS score of 5 points and a moderate to severe case of ophthalmopathy, confirmed on MRI by hypertrophic orbital muscles. At the moment, the patient was aviremic and with a CD4 cell count of 665. The patient was started on pulse therapy with 750 mg of methylprednisolone, continued for 6 weeks, and 500 mg the following 6 weeks. No serious side effects were reported during treatment with steroids. Exophthalmos was the only remaining symptom after treatment, CAS score was reduced to 1 point.
Conclusions
Graves orbitopathy in HIV patients is uncommon and is not well-described in the literature. Many challenges may appear in these patients, especially regarding pharmacological interactions of antiretroviral, antithyroid and steroid drugs. Still, in our particular case, first-line treatment with steroids was efficient in reducing ophthalmopathy symptoms.

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P220

C-reactive protein level in patients with autoimmune hypothyroidism before and after levothyroxine treatment

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Hypothyroidism is one of the most common endocrine disorders. The long-time debatable question is whether patients with subclinical hypothyroidism (SH) should be treated with levothyroxine. Data are contradictory and treatment decision depends on several factors: TSH level, anti-TPO level, age, presence of symptoms etc. Hypothyroidism is associated with cardiovascular disease. Even a minor increase in C-reactive protein (CRP) is considered a cardiovascular risk, therefore evidence of beneficial effect of levothyroxine treatment on CRP could be an argument in favour of therapy. The aim of the study was to assess the level of high sensitivity CRP (hs-CRP) in patients with overt and subclinical hypothyroidism and to evaluate the (potential) effect of levothyroxine treatment on hs-CRP. Parametric data were tested by one way ANOVA and non-parametric data – by Kruskal Wallis test. Effect of treatment was assessed by paired t-test or Wilcoxon signed Rank test. Analysis of frequencies was performed with the use of Pearson Chi-Square tests using Bonferroni-correction for multiple comparisons. $P<0.05$ was considered significant. 37 patients (17 with overt hypothyroidism, OH and 20 with SH) and 37 healthy controls were included in the study. TSH, fT4, total cholesterol (TC), HDL-C, LDL-C, creatinine, creatin kinase (CK) were determined in all participants. hs-CRP was measured at baseline visit, then after 2 and 4 months of levothyroxine therapy. hs-CRP was significantly increased in OH ($P<0.001$) and SH ($P=0.001$) at baseline as compared to controls. hs-CRP significantly decreased in SH (2.2 ± 1.6 mg/l at baseline visit, 1.4 ± 1.1 mg/l after 2 months of treatment, $P=0.017$) and tended to decrease in OH (2.3 ± 1.6 mg/l at baseline visit, 1.6 ± 1.1 mg/l after 4 months of treatment, $P=0.067$*). Mean hs-CRP in the control group was 0.9 ± 0.4 mg/l. Only 17.6 % of patients with OH and 30 % of those with SH had a hs-CR $P<1$ mg/l at baseline visit, as compared to control group, where 71.1 % of persons were at low cardiovascular risk. After 4 months of treatment 41.2 % and 40 % of patients with OH and SH respectively decreased their hs-CR $P<1$ mg/l. Levothyroxine treatment did not change the rest of biochemical biomarkers in patients with SH. Body mass index (BMI) was highest (29.1 ± 3.7 kg/m^2) in the subgroup of patients with hs-CR $P>3$ mg/l and lowest (23.8 ± 4 kg/m^2) in the subgroup of patients with hs-CR $P<1$ mg/l ($P=0.03$), which highlights the role of body weight in inflammation.

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Effects of Growth Hormone Therapy on Thyroid Function in Adults with and Without Concomitant Central Hypothyroidism in Growth Hormone-Deficient Patients

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Introduction
Numerous thyroid function disturbances have been linked to the administration of growth hormone (GH) to GH-deficient patients. There have been reports of anything from increased energy expenditure and improved peripheral thyroxine (T4) to triiodothyronine (T3) conversion to decreased thyrotropin (TSH) sensitivity to thyrotropin-releasing hormone (TRH) stimulation and induction of hypothyroidism.
Objective
GH has an impact on thyroid structure and function. Although goitre is common in acromegalic patients, it can be challenging to evaluate the consequences of GH deficiency (GHD) because hypopituitarism persons with GH deficiency frequently simultaneously have a partial or total deficit of TSH.
Method
Comparing subjects heterozygous for the same mutation (10 men and 9 women; HET group) and subjects homozygous for the wild-type allele [6 men and 10 women; control (CO) group] to subjects with the homozygous mutation in the GHRH receptor gene (GHRHR), the thyroid morphology and serum levels of thyroid hormones in adult members of a large kindred with untreated isolated GHD was compared. The statistical program SPSS/PC 8.0 was used to conduct the statistical analysis. For qualitative variables, values for continuous variables are given as the mean+sd. For the purpose of comparing the three groups, ANOVA was used. The correlation between TV and its determinants was calculated using the Spearman correlation. Statistics were judged significant at $P<0.04$.
Result
Thyroid volume (TV) in GHD participants was lower than in HET and CO subjects. Between the GHD and CO groups' TVs and those of the HET group, it was in the middle. When TV was adjusted for body surface area, the difference between the GHD and HET groups vanished but TV remained less in the GHD and HET groups than in the CO group. When compared to the CO group and HET and CO groups, the GHD group's serum T3 levels were lower and its free T4 levels were greater.
Conclusions
It is possible that GH plays a permissive role in the growth of the thyroid gland because people with severe untreated GHD caused by a homozygous GHRHR mutation and heterozygous carriers of the same mutation have smaller TV than healthy individuals. Additionally, blood total T3 and free T4 levels in GHD participants were lower, suggesting that the deiodinase system may not be functioning as well.

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P222

Prediction and Classification models for Hashimoto's thyroiditis risk using clinical and paraclinical data

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Background
Hashimoto's thyroiditis (HT) is the most common autoimmune disorder and, also, the leading cause of hypothyroidism in iodine-sufficient areas. In recent years, a concept emerged, that thyroid autoimmunity could be associated with low-grade chronic inflammation, which may result in future cardiovascular comorbidities, independent of thyroid function. It is therefore essential to diagnose Hashimoto's thyroiditis as early as possible and to test for thyroid function.
Methods
We recruited 129 participants, including 104 diagnosed HT patients and 25 non-HT controls. Secondly, we collected 12 factors and analyzed their significant differences between controls and HT patients; the clinical factors analyzed were age, family history of autoimmune thyroid disease, personal history of: breast cancer, surgically induced menopause, diabetes mellitus type 2, polycystic ovary syndrome. The paraclinical parameters evaluated were: anemia, hemoglobin, hematocrite values, hypertriglyceridemia, hypercholesterolemia, hyperuricemia, fasting hyperglycemia, abnormal liver function tests. We evaluated the following models: Decision Tree, K-Nearest Neighbor, Extreme Gradient Boost, and Support Vector Machine for classification and regression, as well as neural networks: Artificial Neural Network and Deep Neural Network.
Results
The best model for binary classification was K-Nearest Neighbor, with an accuracy of 85%, sensitivity of 78% and specificity of almost 100%. Concerning regression analysis, we obtained a Pearson coefficient of 97% and an R-squared value of 94% for the Deep Neural Network. Statistical indicators, designed for the regression part confirmed a family history of autoimmune disease, personal history of breast cancer, surgically induced menopause, anemia, hypertriglyceridemia, hyperuricemia, fasting hyperglycemia, and increased alanine aminotransferase values as significant risk factors for Hashimoto's thyroiditis.
Conclusions
The proposed models of machine learning, combined with multiple factors, are efficient for HT diagnosis. These findings suggest screening for autoimmune thyroid disease in metabolic syndrome patients, in breast cancer patients and in women with surgically induced menopause.
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The Association of Iodothyronine Deiodinase Gene Polymorphisms and Hashimoto's Thyroiditis: Does Free T3 Play a Role?
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Introduction
Hashimoto's thyroiditis (HT) is caused by a variety of genes, cytokines, receptors, and environmental factors. A series of enzymes known as type 1 and type 2 deiodinases (D1, D2) are in charge of converting thyroxine (T4) into triiodothyronine (T3). It is believed that the low free T3 (fT3) levels caused by D2 polymorphism may result in thyroid autoimmunity through the induction of inflammation. However, iodothyronine deiodinase (DIO) gene polymorphism and HT in conjunction with fT3 levels have not been thoroughly investigated. In this study, we aimed to examine the relationship between HT and DIO polymorphisms (D1 rs11206244, D2 rs225014, and D2 rs12885300) as well as the effect of DIO gene polymorphisms on fT3 and autoantibody levels (anti-thyroid peroxidase, anti-thyroglobulin, thyroid receptor antibody).
Methods
Participants aged 18-65 years are included in this cross-sectional study. Among 183 participants, 87 is diagnosed with HT, and 96 are healthy subjects. We measured autoantibody levels and thyroid ultrasonography to determine the diagnosis of HT. Peripheral blood samples were collected from all participants for genetic analysis and to measure thyroid function tests. All participant's genomes were analyzed for DIO polymorphisms by PCR-RFLP method. We included only euthyroid HT patients with or without levothyroxine treatment for the evaluation of DIO gene polymorphisms on fT3 levels.
Results
HT patients were found to have D2 rs225014 'TC' and 'CC' alleles more frequently ($P = 0.025$) than in healthy controls. Free T3 levels were shown significantly lower in euthyroid HT patients compared to healthy subjects ($P = 0.007$). In addition, HT patients with D2 rs225014 'TC and CC' alleles were found to have significantly decreased fT3 levels ($P = 0.005$) compared to the healthy subjects. No association was found in the D1 rs11206244, D2 rs12885300 polymorphisms, HT and fT3 levels. None of the DIO gene polymorphisms was associated with the autoantibody levels.
Conclusions
We demonstrated that the D2 rs225014 'TC' and 'CC' alleles were associated with HT. HT patients with D2 rs225014 polymorphism 'TC and CC' alleles exhibited lower fT3 levels compared to the healthy subjects. Our findings support D2 rs225014 polymorphism is linked to HT and that fT3 may function as a potential mediating factor in this connection.
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P224

PAX8-PPARγ rearrangement, galectin-3 immunoreactivity and risk of deep vein thrombosis (DVT) in patients with metastatic follicular thyroid cancer (FTC)
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Introduction
Follicular thyroid cancer (FTC) account for approximately 15% of all thyroid malignancies, with about 65 % being conventional and 35 % Huürthle cell type. Recently a *PAX8-PPARγ* gene fusion was detected in a significant portion of FTCs, some with a chromosomal translocation t(2;3)(q13;p25). The t(2;3) rearrangement leads to an in-frame fusion of the *PAX8* gene, which encodes a transcription factor, with the peroxisome proliferator-activated receptor (PPAR) γ gene. They are able to promote neoplastic cell proliferation and possible hypercoagulability. The number of studies on deep vein thrombosis (DVT) coexist with FTC is limited and medical data are contradictory.
Aim
The aim of the study was to perform genomic analysis of the *PAX8-PPARγ* rearrangement in patients with metastatic FTC and to determine the prevalence and risk factors associated with DVT taking into consideration the status of *PAX8-PPARγ*. We have also analyzed the association between *PAX8-PPARγ* rearrangement and its correlation with galectin-3 immunoreactivity.
Material and Methods
The study included 57 patients who underwent a total thyroidectomy for FTC, aged 38-61 years. The *PAX8-PPARγ* status was detected using Real-time polymerase chain reaction. Diagnosis of the FTC was confirmed with histopathological examination. Diagnostic strategies were evaluated for DVT.
Results and Conclusion
Among 57 patients, only 3 patients (5.3 %) had *PAX8-PPARγ* rearrangement. The FTCs with *PAX8-PPARγ* typically showed immunoreactivity for galectin-3 and tended to present at a younger patient age. In our study, we could not confirm the connection between *PAX8-PPARγ* rearrangement and the occurrence of DVT in patients with metastatic FTC.
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Clinical Characteristics of Differentiated Thyroid Carcinoma with Obesity and Glucose Metabolism
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Objective
To explore the association between body mass index (BMI) and plasma glucose level with pathological features and clinical outcomes of differentiated thyroid cancer (DTC).
Methods
Clinical data of 1264 consecutive DTC patients treated with total thyroidectomy and enrolled at the time of the first ^{131}I treatment from April 2016 to July 2020. The clinicopathological findings were compared in the groups were categorized according to BMI and glycemic disorders. Independent samples t-test, Mann-Whitney U test and χ^2test were employed to compare the correlation between

BMI and plasma glucose level with pathological features and response evaluation of DTC. Logistic regression analysis was used to analyze the independent risk factors for the aggressiveness of DTC.
Results
The analysis according to BMI evidenced overweight and obesity were more frequent in males ($P=0.000$) while patients in the overweight group were older and had higher TNM stage ($P=0.000$, 0.004). The proportion of patients with bilateral tumors was higher in the overweight and obese group ($P=0.001$). However, there was no significant correlation between BMI and lymph node metastasis, TNM stage, T stage, N stage, M stage and response evaluation ($P>$ 0.05). Diabetes group are older than the other groups, and the proportion of men and bilateral tumors were found to be significantly higher ($P=0.000$, 0.000, 0.045). Compared with the normal blood glucose group, the BMI index of patients with prediabetes and diabetes is higher, and the BMI index of patients with prediabetes is the highest ($P=0.000$). The T stage and TNM stage were higher in the diabetes group ($P=0.032$, 0.000). However, there was no significant correlation between glycemic status and lymph node metastasis, N stage, M stage and response evaluation ($P>$ 0.05).
Conclusions
DTC patients with high BMI and diabetes may have more aggressive incidence. But BMI and glycemic status has no correlation with the response evaluation of DTC patients.
Key words
Differentiated thyroid carcinoma; Body mass index; Glycemic status; Obesity
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A retrospective study on the immunocitochemistry profile of benign thyroid nodules unresponsive to thermal ablation

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Objective
Thermal ablations (TA) are gaining ground as alternative options to conventional therapies for symptomatic benign thyroid nodules. Little is known on the impact of nodule biology on the outcomes of TA. The aim of our study was evaluating the baseline immunocytochemistry profile of thyroid nodules that are poorly responsive to TA, in order to identify potential predictors of treatment response.
Methods
we retrospectively selected by propensity score matching two groups of patients with benign thyroid nodules treated with TA, namely CASE (patients who did not respond to TA and were later surgically treated) and CNT (patient who responded to TA). The fine-needle aspiration cytology (FNAC) slides obtained before TA were stained for Galectin-3, HBME-1, CK-19, and Ki67.
Results
In both groups, patients were predominantly females in their mid 40s, their nodules measured 17 mL (range 10-55) and were mostly solid (that is with a solid component $>$ 90%) and non-functioning. Treatment modality was most often laser ablation (87-92% of cases). There were no differences in terms of energy delivered. Benign nodules of the CASE group ($n=24$), did not express CK-19 while expressed more frequently Ki-67 as compared to the CNT group ($n=26$). CK-19 appeared to be the most sensitive marker (high NPV), whereas Ki-67 was the most specific (high PPV) for retreatment and regrowth. When we combined CK-19 and Ki-67, the AUC was of 0.69 (0.57-0.81) for retreatment, and it had a sensitivity, specificity, PPV and NPV of 32%, 91%, 78%, and 58%.
Conclusions
CK-19 expression was predictive of no regrowth/retreatment. If confirmed, this finding could provide a rapid and inexpensive information about the potential outcome of TA on benign thyroid nodules. As CK-19 is more frequently expressed in adenomatous hyperplasia, it could be speculated that these nodules, rather than follicular adenomas, are better candidates for TA.
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Radioactive Iodine Treatment in Hyperthyroidism is Associated with Increased Body Weight

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Introduction
Definitive treatment of hyperthyroidism with Radioactive Iodine (RAI) ablation therapy has been associated with weight gain from RAI induced hypothyroidism. Literature on weight data of post-RAI patients following normalisation of thyroid function is equivocal.
Objective
We undertook a retrospective study to evaluate the effect of RAI on weight in Hyperthyroid patients in University Hospitals of Leicester NHS Trust (UHL).
Methods
Retrospective electronic records review on 'Clinical Workstation' database was undertaken to identify RAI-treated patients. We limited the electronic search to adults (>16 years old) who received at least one session of RAI for hyperthyroidism at UHL from 2003 to 2022. We only included patients with measured weight in the euthyroid state before and after RAI. We excluded patients with thyroid carcinoma due to direct effect of cancer on weight regardless of thyroid function. Euthyroid state was defined as normal thyroid function test and/or absence of clinical features of hyper/hypothyroidism at the time of body weight measurement.
Results
Of the 575 patients undertaken RAI treatment, $n=$ 51 patients were included to analyse as they fulfilled the criteria; a) had pre- and post-RAI weight data within 4-weeks of clinical encounter, and b) TSH normal. Majority were females (Female:Male = 42:9). Mean age = 57 years. Aetiology was Graves' disease in 20, Non-autoimmune in 31 patients. Mean duration of follow up was 52 months. All 51 patients were rendered euthyroid on anti-thyroid medications (ATDs) prior to definitive treatment with RAI. Mean weight gain was 4.02 kg (5.3%) following RAI treatment. Autoimmune hyperthyroidism patients gained 3.05 kg (4.2%) compared to 4.65 kg (6%) in the non-autoimmune group. Males appear to have gained more weight than females following RAI, 7.56 kg (8.2%) and 3.26 kg (4.5%), respectively.
Discussion
RAI appears to cause weight gain across gender and age groups. However, weight documentation during clinical encounters has been inconsistent. This study did not account for confounders like lifestyle, co-morbidities and medications that potentially impacted body weight and finally, it's unclear if there's an element of weight overcorrection prior to TSH normalisation from hypo/hyperthyroidism. We took findings of this study to set up a prospective cohort study looking for RAI impact on body weight across aetiologies, interventions (ATDs, surgery and RAI) and comorbidities.
Learning points
1. RAI treatment appears to cause weight gain across gender and age categories.
2. Patient information leaflet warning of potential weight gain side effect ahead of RAI treatment may influence treatment choice and help adopt preventative dietary and life-style measures.

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P228

The role of thyroid autoimmunity in assisted reproduction outcome-not yet solved puzzle

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Background
hyroid autoantibodies cross blood-follicle barrier in titer dependent manner and may change oocyte microenvironment with adverse effects on implantation or

post-implantation period. Thyroid autoimmunity (TAI) interfers with pregnancy course and newborn anthropometry in pregnancy achieved by assisted reproduction (ART).
Objective
To light upon pregnancy course outcomes and newborn anthropometric characteristics regarding TAI in ART programme.
Methods
The course of clinical pregnancy achieved in 24 women undergoing ART was observed and pregnancy and newborn outcomes compared in two groups divided by the presence of TAI.
Results
In the study population, 33.3% were TAI positive and 66.7% TAI negative women. The special interest was adressed on anti-thyroglobulin antibodies with the important difference in serum, as expected, but in follicular fluid, $P<0.001$. Number of retrieved oocyte, number of embryos, *top quality* and embryo transferred were not significantly different between the groups, but higher percentage of good quality oocytes in TAI negative group were noticed (70.9% vs 81.5%, $P=0.053$), without affecting fertilization and implantation rates. Live birth rate was 96.0%, with preterm birth 16.7% and term birth rate 70.8%. Groups were no different comparing the rate of twin pregnancy, early, late miscarriage and preterm birth. Maternal complications, gestational diabetes mellitus or pregnancy induced hypertension, were present in 23.8% with no difference between the groups. In TAI positive group newborns had higher birth weight ($P=0.001$) and lenght ($P=0.008$). No congenital malformations in newborns were noted.
Conclusions
The study pointed out no adverse effects of TAI on ART achieved pregnancy outcomes, regardless the higher percentage of good quality oocytes in the women without TAI, but TAI could affect newborn anthropometry.

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Severe malnutrition associated with amyloid goiter: A case report

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Background
Amyloidosis is defined as the accumulation of amorphous, proteinaceous material in different parts of the body. It can be primary or secondary, having decreased the incidence of this last one due to the current therapeutic landscape of infectious and autoimmune diseases. This material can be deposited in the thyroid gland resulting in an enlargement known as Amyloid goiter. Although amyloid infiltration in thyroid is common, the occurrence of clinically enlarged thyroid owing to amyloid deposition, leading to goiter, is an extremely rare phenomenon.
Case Presentation
A 72-year-old woman with chronic pyelonephritis and hearth failure with preserved ejection fraction due to hypertrophic cardiomyopathy was referred to our outpatient clinic presenting severe malnutrition related to an enlarged thyroid gland with compressive symptoms (dysphagia). Thyroid function test results were in the normal range and serum thyroid autoantibodies were undetectable. Cervical ultrasound showed a diffusely swollen thyroid and fine-needle aspiration (FNA) cytology showed a pattern consistent with lymphocytic thyroiditis. Neck CT-scan again showed symmetrically enlarged thyroid lobes up to 107 mm at his largest diameter with retropharyngeal extension, surrounding trachea and esophagus. Abdomen CT-scan revealed a substantial dilation of calyces with lithiasis, a marked parenchymal atrophy with significant perirenal fat thickening, perirenal effusion and retroperitoneal adenopathies in his right kidney. Prior to surgery, the patient needed parenteral nutritional support. After preoperative work-up, total thyroidectomy was performed without complications. The histopathological study revealed the presence of amorphous protein aggregates that was stained with Congo-Red dye and the immunohistochemistry study was positive for Amyloid A and P proteins. The patient was later diagnosed with secondary amyloidosis due to xanthogranulomatous pyelonephritis.
Conclusion
Amyloid goiter is an extremely rare entity. Secondary amyloidosis must be considered in the differential diagnosis of thyroid enlargement, specially those with rapid onset, and particularly in patients with a history of chronic infections or inflammatory disorders predisposing to amyloid deposition. FNA biopsy should be performed to exclude malignancy and thyroidectomy is necessary for definitive diagnosis.

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Exogenous Testosterone May Have A Effect on Thyroid Volume İn Trans-Men

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Purpose
Thyroid autoimmune diseases occur more frequently in women than men. A previous study reveals that exogenous testosterone may have a protective effect on thyroid autoimmunity in men with Hashimoto's thyroiditis. But no study has determined whether sex hormones produce any effect on thyroid antibody titreş in women. The primary study aim was to assess whether exogenous testosterone affects thyroid autoimmunity in trans-men with increasing testosterone levels.
Methods
We designed this study as a single-center prospective study. We included 60 drug-naive trans men, and the control group comprised 26 healthy cisgender women. We measured and compared hormone profiles and metabolic parameters in the two groups initially and after six months under exogenous testosterone. Each participants underwent a preliminary ultrasonography and it was investigated whether there was any abnormality such as a nodule or parenchymal heterogeneity. The thyroid gland was scanned in three dimensions. Depth, width (in transverse plane), and length (in longitudinal plane) of each lobe were measured. Volume of each lobe was calculated using the formula, volume (mL) = π/6 x width x depth x length (15). Total volume was determined as the sum of the volumes of the lobes except for the isthmus.
Results
In patient group, there was no significant difference according to TSH levels (P 0.308) and fT4 levels (P =0.650) before and after treatment. But total testesterone levels and thyroid volume (7.62 $\pm$ 2.57 mL and 8.37 $\pm$ 2.74 mL; before and after treatment, respectively) were significantly higher after treatment ($P<0.001$ and $P=0.042$, respectively). The existence of thyroid nodule didn't significantly change before and after the treatment ($P=0.791$)
Conclusion
This study is the first one to have shown that exogenous testosterone may have a effect on thyroid volume in trans men but doesn't cause an increase in thyroid nodul formation. Testesteron's effect on thyroid needs to be followed for a longer period to determine accurately.

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Differences between Unilateral and Bilateral Graves' Orbitopathy. An observational study

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Introduction
Graves' Orbitopathy (GO), the most common extrathyroidal manifestation of Graves' disease (GD), usually presents bilateral disease. However, a minority of patients present with unilateral disease, the prevalence of which is between 4,5% and 14%. The aim of our study is to evaluate the specific demographic and clinical characteristics and potential differences between bilateral and unilateral GO, and the association with disease activity and severity.
Materials and Methods
We conducted an observational study in the outpatient clinic of autoimmune endocrinopathies of the Department of Pathophysiology at Laikon University Hospital. Patients with GD and GO were included in the study. Demographic and clinical characteristics were recorded. We evaluated disease activity with CAS and severity based on EUGOGO consensus. All patients were assessed for TSI levels, TgAbs, TPOAbs and proptosis with Hertel exophthalmometer. Data collected were compared between the two groups of bilateral and unilateral GO.

Results
A total of 102 patients were analyzed. Of whom, 19,6 % presented with unilateral GO. In the bilateral GO patient group mean age was 52.9 ± 13.2 years and 75.6% of them were females. Regarding disease severity, mild, moderate and severe disease accounted for 22.5%, 58.8% and 18.8%, respectively and 64,6% had active disease. The median TSI levels was 9.670 IU/l and the majority of them were negative for TgAbs. Median proptosis for the right eye was 21mm and 20mm for the left. 58% presented with diplopia and 18,3% with strabism. In the unilateral GO patient group the mean age was 56,1 ± 10,7 years and 60% of them were females. Regarding disease severity 40% presented with mild, 35% with moderate and 25% with severe disease. Active disease accounted for 50% of patients. Median TSI levels was 6,55 IU/l and median proptosis was measured 19mm for the right eye and 18,5mm for the left. Diplopia was present in 60% and strabism in 30 %.
Conclusion
In our study, in bilateral GO group the majority of patients presented with moderate disease whereas in unilateral GO group with mild disease. Mean TSI levels and median proptosis were higher in the bilateral GO group. Active disease presented more frequently in bilateral than in unilateral GO group.

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Efficacy and Safety of Ultrasound-Guided Percutaneous Polidocanol Sclerotherapy Vs Percutaneous Ethanol Injection in Benign Cystic Thyroid Nodules: Preliminary Results

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Introduction
Percutaneous Ethanol Injection (PEI) is well known treatment for benign cystic thyroid nodules; however, local pain is common side effect.
Objective
To compare between efficacy and safety of Percutaneous Polidocanol Sclerotherapy (PPS) vs PEI.
Patients and methods
We included 60 patients -with mean age 32 years- have benign thyroid nodules (9 of them were males). They were divided into 2 groups; *group 1* with 30 patients ablated by PEI as a control group & *group 2* with 30 patients ablated by PPS. The mean initial volume of nodules was estimated, and volume reduction rate (VRR) after 1 month & 3 months were compared. Moreover, compressive & cosmetic score were compared before and 3 months after ablation in addition to adverse events.
Results
The mean initial volume was 23.23 ± 6 ml in group 1 vs 24.57 ± 5 ml in group 2 (*P* value: 0.38). No statistically significant difference between 2 groups regarding VRR after 3 months (*P* value: 0.9). Local pain is statistically significantly higher among group 1 (*P* value: <0.001). Hoarseness of voice was found to be higher among group 1 (5 patients vs 1 patient). Fever after procedure was higher in group 2 (7 patients vs 1 patient)
Conclusions
PPS have similar efficacy to PEI in ablating benign cystic thyroid nodules with minimal side effects.

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Impact of SARS-COV-2 infection on the endocrine system: a case series

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Introduction
There is evidence that SARS-COV-2 infection can result in development of endocrine disturbances. Expression of the angiotensin-converting enzyme 2, which is postulated to be at the center of the pathogenesis of COVID-19, has been reported in various endocrine tissues.
Case Series
We retrospectively analyzed 12 patients with recent history of SARS-COV-2 infection: 5 cases with subacute thyroiditis (SAT), 2 cases with Graves' disease, 2 cases with adrenal insufficiency, 2 cases with secondary amenorrhea and 1 case with male hypogonadism. Out of 5 patients with SAT, 3 were females and 2 males (34-57 years). SAT developed after a median of 12.8 weeks following COVID-19 infection resolution. The main presenting symptoms were neck pain and palpitations. Thyroid function tests showed overt hyperthyroidism in all patients. Treatment was initiated (4 patients with prednisone, 1 patient with ibuprofen) and within 6 weeks, all patients were asymptomatic, with normalization of inflammatory markers, 3 out of 5 were euthyroid, whereas 2 were hypothyroid. Two female patients were diagnosed with Graves' disease right after COVID-19 infection (age 31 respectively, 39). Thyroid function tests showed transient hyperthyroidism in the first patient and overt hyperthyroidism in the second patient, with positive thyroid stimulating hormone receptor antibody (TRAb, 3.18 UI/l, respectively >40 UI/l, range 0-1.75). Only the first patient associated Graves' ophthalmopathy. The second patient had persistent atrial fibrillation and a 4-weeks follow-up showed normal thyroid function under treatment with methimazole. A 20-year-old male presented with chronic fatigue, nausea and vomiting 4 months following COVID-19 infection. He was diagnosed with primary adrenal insufficiency based on elevated ACTH level (1250 pg/ml, range 3-66), low cortisol level (2 µg/dl, range 4.82-19.5) and presence of 21-hydroxilase antibodies. Another 31-year-old female patient presented with orthostatic hypotension 14 months following COVID-19 infection. Laboratory tests revealed elevated ACTH level (195 pg/ml) and suboptimal stimulation after intramuscular 250-µg cosyntropin test. COVID-19 might have contributed to clinically relevant disease progression. Two female patients were diagnosed with secondary amenorrhea after COVID-19 infection (age 28, respectively 35) with good response to progesterone treatment. One male patient was diagnosed with transient hypergonadotrophic hypogonadism following COVID-19 infection. A 2-weeks follow-up showed normalization of serum FSH, LH and testosterone.
Conclusion
The endocrine system is vulnerable to perturbation from SARS-CoV2 infection, therefore among other symptoms and late complications, hormonal parameters should be monitored in these patients. Long-term effects of COVID-19 on the endocrine system remains to be investigated.

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Lower expression of miR-21 is related to multifocal lesions of papillary thyroid carcinoma

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Introduction
Multifocality empirically is often treated as a risk factor for aggressive course of papillary thyroid carcinoma (PTC), encouraging aggressive treatments. However, inconsistency and even contradiction in a literature is present concerning the role of tumor multifocality in clinical outcomes of PTC. Therefore, the prognostic value of multifocality of PTC remains controversial, creating a difficulty in the current clinical management.
Methods.
We analyzed miR-146b, miR-21, miR-221, miR-21, and miR-181b in formalin fixed paraffin embedded PTC tissue samples of 312 individuals and evaluated their expression relationship with multifocality of a tumor.
Results.
Multifocality was observed in 68 (21,7%) of the PTC patients. Patients with multifocal lesions had significantly lower expression of miR-21 than those with unifocal ($n=224$) lesions ($P<0.011$) in our study. MiR-146b, -221, -222, 181b expression did not statistically significantly differ between these groups.
Conclusions
Our results suggest that lower expression of miR-21 is related to multifocal lesions. Data from numerous other studies confirm that miR-21 is usually overexpressed in PTC associated with aggressive clinicopathological features. So, our findings of lower miR-21 expression let us to hypothesize, that multifocality might not be a risk factor of poor PTC prognosis.

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P235

Role Of liothyronine + Levothyroxine combination therapy in 70 overweight/obese patients with TSH between 2.5-5 unable to loose weight

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Aim
To asses the role of Liothyronine (T3) + Levothyroxine combination (T4) therapy in 70 overweight/obese patients with Thyrotropin Stimulating Hormone (TSH mIU/ml) between 2.5-5 who were unable to lose weight.
Methods
Between Jan' 20 - Jan' 21, 70 overweight/obese patients with TSH 2.5 -5 performed on ± 2 occasions ± 4 weeks apart were retrospectively analyzed. 24% {17/70} had TSH 2.5-2.99, 37% {26/70} had TSH 3-3.99 & 39% {27/70} had TSH 4.0-4.99. Twenty% {14/70} were anti-topoisomerase antibody (TPOAb) +ve of which 5.71% had TSH 2.5-2.99, 5.71% had TSH 3-3.99 & 8.57% had TSH 4-4.99. Eighty% {56/70} were TPOAb -ve. They were referred by a nutritionist for inability to lose weight despite being on > 3 months weight loosing regimen (<1000Kcal/day). Protocol: Patients were initiated T3 25 mg/day along with varying doses of T4 to help optimize the TSH (lower limit of normal reference range) & followed 2-3 mths for 6 mths for clinical/cardiac parameters: weight (W-kg), body mass index (BMI-kg/m^2), systolic BP (SBP-mm of Hg), diastolic BP (DBP-mm of Hg), TSH, Lipid profile mg/dl (TC, LDL-C, TG, HDL) & Hs-CRP mg/l. Continuous variables were analyzed using paired & unpaired t-test expressed as mean ± standard error. For interaction between drug class, ANOVA was used & p value <0.05 was considered significant (S).
Results
Baseline (B) characteristics: Avg. age 39.89±11.215yrs, Female/Male ratio 62/8 (88.6%/11.4%), avg. BMI 29.0409±7.29339, SBP 119.79±15.752, DBP 80.37±12.040, TSH 3.824707±0.9896442, TC 184.3203±39.52749, LCL-C 116.6784±38.96588, hs-CRP 4.5114±5.59016. Differences between B to 6 months: S reduction in W (1.7500±0.4796, p-0.001), BMI (0.80243±0.21892, p-0.000), TSH (2.2562429±0.2213319, p-0.000), TC (17.85610±4.93128, p-0.001), LDL-C (17.09672±5.06238, p-0.001) were seen, with no changes in SBP, DBP, TG, HDL, hs-CRP.
Conclusion
T3/T4 combination therapy is effective in initiating weight loss and improving lipid profile in patients with TSH between 2.5-5, without any adverse effect on SBP/DBP. Symptomatic patients with TSH between 2.5-5 can be initiated T3/T4 combination therapy as it leads to both weight loss and improvements in TC & LDL which might have beneficial long term cardiovascular effects.

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Clinical and Biochemical Comparative Evaluation of Thyroid Hormone Replacement in Patients with Hypothyroidism Due to Autoimmune Thyroiditis and Total Thyroidectomy

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Aim
Hypothyroidism is a common chronical disease worldwide, leading to a lifelong metabolic slowdown that can have a significant negative impact on the quality of life, both physiologically and psychologically. Despite achieving euthyroidism with replacement, there is evidence that symptoms persist. In this study, we aim to examine the effectiveness of thyroid hormone replacement and the effect of autoimmunity from a clinical-biochemical point of view by evaluating the euthyroidic patients both due to autoimmune thyroiditis or total thyroidectomy comparatively.
Material and Method
The study is a prospective cross-sectional study consisting of a total of 60 patients and 30 healthy control individuals. Of 60 patients, there are 30 cases diagnosed with autoimmune thyroiditis and 30 patients with total thyroidectomy who applied to the internal medicine and endocrinology outpatient clinics of our hospital. The data was collected and maintained with a patient information form, which includes the sociodemographic characteristics, vital signs and clinical characteristics of the participants, the Billewicz Score in which hypothyroid-specific symptoms and signs are questioned, and the international SF-36 Quality of Life Scale in which the status of the quality of life is questioned. In addition, biochemical and hormonal profiles were measured and recorded.
Results
Weekly LT4 dosage was found to be higher in thyroidectomy-induced hypothyroidism group, serum fT4 levels were also statistically significantly higher in this group, whereas it was revealed that there was no difference in serum fT3 levels. There was a negative correlation between LT4 dose and SF 36 mental health and social functionality sub-parameters. Serum cholesterol levels were higher in the autoimmune thyroiditis group, and blood pressure levels were higher in the thyroidectomized group. There was no significant difference between the two patient groups in terms of Billewicz sub-parameters and total score classifications of hypothyroid patients. Similarly, physical function, physical role disability, emotional role difficulty, energy/vitality, mental health and general health perception, which belong to the SF-36 life quality scale sub-parameters, were considerably lower than the control group.
Conclusions
According to the data obtained from the study, while autoimmunity do not have an additional contribution to clinical, biochemical deterioration and quality of life. Patients with hypothyroidism should be evaluated periodically in terms of symptoms and quality of life, even though they become euthyroid.

Keywords: Hypothyroidism, autoimmune thyroiditis, L-thyroxine, quality of life
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Analysis of types of thyroid surgery before and after COVID19 pandemics

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Introduction
Thyroid surgery usually performed in 20% when traditional drug therapy was not effective, or development severe complications, or high risk/presence of cancer. New infection COVID19 affected whole body and probably thyroid results changes in clinical future and treatment. The aim of our study were investigate if frequency and type of thyroid surgery affected by COVID19 pandemics.
Material and methods
We analysed and compared data from one medical centre about thyroid surgery frequency and type before and after COVID19. Data of patients who were admitted for thyroid surgery in Vitamed Medical hospital in Tashkent from 2019 and 2022 were collected and analysed year by year.
Results
Patients chart of 525 people whose were admitted for thyroid surgery during 2019-2022 years were analysed. 86% woman and 14% men among them with average age 45.5±2.5 years old. Most part (60%) of all thyroid surgery were done for nodular goiters and 20% were done for thyroid cancer. Interestingly, before COVID19 pandemics nodular goiters were frequent causes and consisted 71% of all thyroid surgery. After COVID19 pandemics nodular goiters still frequent cases among all thyroid surgery but its pattern had decreased and consisted 57%. We found that surgery by thyroid cancer were increased after pandemics. If thyroid cancer were represented 14% of thyroid surgery cases before pandemics after pandemics the portion gradually increased to 20%. Moreover, gender distribution also were changed with increasing number of males after pandemics. It had shown mostly in thyroid cancer group, where male/female ratio was 1:13 in 2019 and become 1:3 after COVID19 pandemics.
Conclusions
Types of thyroid surgery were varied after COVID19 pandemics with gradually increasing number of thyroid cancer and also increasing number of male patients.

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May Concomitant Thyroid Autoimmunity be Associated with Better Prognosis in Thyroid Papillary Carcinoma?

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Aim
The association between thyroid autoimmunity and thyroid cancer has long been suggested, in addition whether and how the concurrent thyroid autoimmunity with Papillary Thyroid Carcinoma (PTC) affects clinicopathological features and prognosis is a matter of debate. In the present study, we aimed to evaluate the laboratory data, cancer characteristics and prognosis of PTC patients with and without thyroid autoimmunity.
Materials and Methods
Data of 2276 patients who underwent total thyroidectomy in our hospital from 2012 to 2022 was analysed. Total 202 patients diagnosed as PTC whose full data could be accessed were included in the study. The demographic, clinical and pathological features were recorded. Thyroid autoimmunity is defined as presence of antibodies against Thyroglobulin (Tg), thyroid peroxidase (TPO), and/or TSH receptor (TR).
Results
Mean age of patients was 46.67 ± 12.8/year, Majority of patients were female ($n = 165$, 81%). Autoimmunity was positive in 73 patients (36 %). Hundred seven patients (53%) were papillary microcarcinoma. Disease age in the majority of patients was between 1-5 years ($n = 161$, 79.7%). There was a statistically significant difference ($P < 0.001$) in postoperative Thyroglobuline measurements when autooimmune positive patients were compared with autoimmunity negative patients (5.522 ± 26.916 IU/MI and 16,489 ± 52.26 IU/MI respectively). The patients with pre-op Anti-Tg value > 115 IU/MI were excluded, and postoperative thyroglobuline levels remained lower in antiTPO and/or TRAb positive cases (mean post-op TG was 18.12 ± 55.9 in anti-TPO and TRAb negative group, the mean post-op TG level was 4.39 ± 11.05 in Anti-TPO and/or TRAb positive group) ($P < 0.001$).
Conclusions
Since the post-op Tg level is significantly low in autoimmunity positive patients, independent of pre-op anti-Tg elevation, it can be suggested that the prognosis of PTC may be better in individuals with autoimmunity with high anti-TPO antibody titers. However, larger and prospective studies are needed to clarify the relationship between PTC and autoimmunity

Keywords
Papillary Thyroid Cancer, Thyroid Autoimmunity, Anti-TPO
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2D-SWE PLUS in the assessment of thyroid malignancy

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Our study assesses the diagnostic performance of 2D shear-wave elastography plane-wave ultrasound (2D-SWE PLUS) in detecting thyroid cancer. Using conventional ultrasound (2B-mode) and 2D-SWE PLUS with SuperSonic Mach30 equipment, 270 thyroid nodules were assessed (Supersonic Imagine, France). In every instance, the outcomes and the pathology reports were compared. 69 (or 25.5%) of the 270 nodules were malignant. 2D-SWE PLUS parameters demonstrated great diagnostic accuracy. The best parameter for the 2D-SWE PLUS was the mean elasticity index (AUROC 0.912); with a cut-off value of 30 kPa, it accurately predicted thyroid cancer with a sensitivity of 83% and a specificity of 98%.

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Fatal bleeding and thrombosis in a patient with autoimmune primary hypothyroidism

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Introduction
Thyroid diseases have been known to cause haemostatic changes, either tendency to bleeding or thrombosis. We report a case of a patient with primary hypothyroidism presenting with spontaneous bleeding and jugular thrombosis.
Case report
An 85-year old patient with no medical history was admitted to the endocrinology department with primary auto-immune hypothyroidism. Hypothyroidism was suspected because of severe loss of weight and appetite, constipation and an extreme fatigue and lethargy. Initial TSH levels were>180 µUI/ml, FT4 was at 0pmol/l and morning serum cortisol was at 81ng/ml. Thyroid Peroxydase antibodies were at 643.2 UI/ml (Normal range <9UI/ml). Upon admission, patient was lethargic, had macroglossia and normal blood pressure. No bruising or spontaneous bleeding were noted or reported by the patient. The patient was started on 20 mg of hydrocortisone, and L-thyroxin was progressively initiated at the dosage of 12.5µg daily. Further work-up found megaloblastic anemia at 6,9g/dl along with moderately low level of Platelets at 111 000/µl. Prothrombin time (PT) was normal. On the sixth day of in-hospital stay, the patient presented a mild traumatic bruising on the right arm. Platelets count was normal (170 000/µl) and PT was normal again. CT scan showed an abdominal and pleural effusion, thrombosis of the left jugular vein and an aneurysm on the right iliac artery with partial thrombosis. The patient was started on low dose aspirin. However, the bruising extended to the right shoulder and thorax thus aspirin was discontinued after 2 days. The patient quickly developed unexplained neurological distress, hypoxemia and was started on large spectrum antibiotic. However, death occurred on the 21st day after admission.
Discussion
The association of bleeding state and thrombosis in our patient is remarkable. Overt hypothyroidism usually leads to tendency de bleeding due to a hypocoaguable state. This can be related to a decreased platelets count, an alteration of their aggregation and agglutination, and decreased levels of von Willebrand factor antigen and several multiple coagulation factors. Subclinical hypothyroidism, autoimmune thyroid disorders and hyperthyroidism are on the other hand associated to increased levels of fibrinogen thus a tendency to hypercoaguablity. These disorders are usually corrected after hormonal therapy. However in our case, spontaneous bleeding manifested and extended after initiation of L-Thyroxin. The use of aspirin was short in duration and could not explain its extension. No other cause for these haemostatic disorders was identified in our case. Prospective studies of thromboembolic states in auto-immune hypothyroidism are warranted.

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Investigations on fibroblast growth factor 21 and lipid parameters in patients with Hashimoto thyroiditis

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Background
Fibroblast growth factor 21 (FGF21) is a hormonal regulator of lipid and glucose metabolism exerting protection against atherosclerosis by multiple actions on the blood vessels, liver, and adipose tissues. Enhanced FGF21 production in diabetes and obesity reduces the level of LDL-C and triglycerides by suppression of hepatic SREBP-2. Hypothyroidism has also been shown to have unfavorable effects on atherogenesis and dyslipidemia. To date, the association of lipid parameters and FGF21 levels in autoimmune thyroiditis has not been studied.
Subjects and methods
We enrolled one hundred and ten patients with autoimmune thyroiditis (9 males, 101 females, mean age 49 ± 17 years, median BMI 25.6 (23.7-31.4) kg/m2) with various thyroid hormone status from hypo- to hyperthyroidism. Serum FGF21 concentrations were determined with enzyme-linked immunosorbent assay (ELISA). Thyroid hormone levels, anti-thyroperoxidase concentration and lipid parameters were measured by routine laboratory methods.
Results
Median serum FGF21 level was 81.4 (34.9-151.9) pg/ml, LDL-C was 3.2 (2.6-4.0) mmol/l, HDL-C was 1.6 (1.3-1.8), triglyceride was 1.3 (0.9-2.0) mmol/l, TSH was 2.8 (1.3-4.7) mU/l, while mean total cholesterol level was 5.3 ± 1.1 mmol/l. Mean fT3 and fT4 were 4.58 ± 0.71 and 17.8 ± 3.7 pmol/l, respectively. Significant positive correlations were found between age, BMI, total cholesterol, triglyceride, LDL-C, ApoB100, nonHDL cholesterol and FGF21 levels, while there was a significant negative correlation between fT3 and FGF21 levels. According to multiple regression analyses fT3 level is not a significant predictor of FGF21 or lipid levels.
Conclusions
The significant correlations between FGF21 and lipid parameters indicate the link between FGF21 regulating pathway and lipid metabolism in patients with autoimmune thyroiditis, regardless of thyroid function.

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P242

Thyroid manifestations in two different genetic syndromes

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Introduction
The sensitivity of tissues to thyroid hormones can be impaired rarely, either due to the genetic anomalies of the thyroid hormone metabolism and transport. Consequently, the relative triiodothyronine(T3), thyroxine(T4), and reverseT3(rT3) levels get disturbed and different clinical manifestations ensue. Two recently admitted cases are briefly described.
First Case
A 32 yrs old Saudi housewife, had been admitted to our hospital on 05.01.2023, with 2 days history of lower limb pain and weakness. The patient had a past history(2015) of metastatic Papillary thyroid carcinoma(status post total thyroidectomy + radiotherapy with iatrogenic hypoparathyroidism). In 2017, she was diagnosed to have Myelin Oligodendrocyte Glycoprotein Antibody disease(MOGAD)[history of radicular lower-limb pain, paresthesiae, pseudoseizures, urinary urgency and incontinence, pain and temperature deficits in left upper & both lower limbs & positive MOG antibodies (1:40) (EEG, NCV, EMG, CT & MRI normal). It was followed by recurrent, bilateral granulomatous, Panuveitis (since 2019). The patient also had fibroadenoma left breast dyslipidemia and left sensorineural deafness(after radiation, followed by cochlear implantation). She was on regular daily oral Thyroxine150ug, Prednisolone, Mycophenolate, along with low dose Calcium & Vitamin D. Hemodynamically stable. BMI 26.53 kg/m^2 S. Ca + +1.98mmol/l(2.1-2.55), Mg + +0.88mol/l(0.7-1.10), Phosphorus 1.61 mmol/l(0.81-1.45), ALP 53U/l(35-104), PTH 1.36pmol/l(1.6-6.9), Vit. D 27.6nmol/l, TFTs[TSH 130mIU/l(0.25-5), FT4 6.43pmol/l(12-22)], Thyroglobulin 0.04ng/l(3.5-77). Rest of the labs-normal The patient got improved after the correction of hypocalcemia. Oral calcium & Vitamin D doses were optimized. Thyroxine was increased to 175ug/d.
Second Case
The second patient(admitted on 21.12.2022), was a 17yrs old, single, Saudi male(recently transferred under adult care), having Lipopolysaccharide responsive beige-like anchor protein gene mutation(LRBA),[with chronic diarrhea, malabsorption, electrolyte imbalance, iron deficiency anemia, chronic gall-bladder sludging & failure to thrive]. He also had multiple drug allergies. The patient was on regular total parenteral nutrition for 10 yrs, but there was some disruption before the admission. He had a past history of frequent ICU admissions due to TPN line sepsis (MSSA bacteremia in April,2022), electrolyte derangements (had cardiac arrest 2yrs ago). He was taking oral thyroxine, calcium, Vitamin D & iron supplement. Vitally stable. Weight 13.2 kgs. Stunted growth, but mentally like an adult. CBC[Hb%9.1g/l[13-18], MCV 63.6fl, TLC 18.17 x10^9/l (78%neutrophils)(4-11), PLTs 656x 10^9/l(14-450)], LFTs mildly deranged, Blood gases(pH 7.17, PCO2 26mmHg, HCO3-18mmol/l, Corrected Ca + +1.76 mmol/l (2.1-2.55), Phosphorus (0.65mmol/l(0.85-1.6), ALP 226U/l(55-149), Mg + +0.46mmol/l(0.7-1.1), Vit. D 40.5nmol/l ($\leq$ 25-severe deficiency), S. Proteins 53.10g/l(64-83), Albumin 33.2g/l(32-54), TFTs[TSH 8.18mIU/l(0.25-5), FT4 9.26pmol/l(12-22)], Random Glucose 4.1mmol/l(3.9-5.8). The patient's deficient electrolytes got corrected back to normal with replacement, I/V fluids and resumption of his TPN. Afterwards he was discharged home.
Conclusion
Thyroid involvement, although rare, but has been reported in MOGAD & LRBA gene defect.

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P243

Amiodarone-Induced Thyroid Disorders Not Uncommon

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Introduction
Amiodarone is a highly effective drug, used for the treatment of arrhythmias. However, it can cause either hypothyroidism or thyrotoxicosis. It leads to alterations in thyroid gland function or thyroid hormone metabolism, due to its high iodine content. Amiodarone-induced hypothyroidism is common in countries with high iodine dietary intake, and Amiodarone-induced thyrotoxicosis is more prevalent in regions with low iodine dietary intake. A large amount of iodide released during the metabolism of Amiodarone causes the so-called Wolff-Chaikoff effect, in which there is a blockage of thyroidal iodide uptake and thyroid hormone biosynthesis. Here we report two cases of Amiodarone-induced thyrotoxicosis and one case of Amiodarone-induced hypothyroidism.
Cases
1) A 65-year-old male patient with a background of long-standing atrial fibrillation was on treatment with Amiodarone. He was subsequently diagnosed with dilated cardiomyopathy resulting in cardiac failure. A year later, the patient presented with thyrotoxicosis (likely secondary to Amiodarone) blood test showed FT4 20pmol/l, TSH $<$0.01 mIU/l. He was treated with carbimazole, and Amiodarone was discontinued. 2) A 72-year-old man presented to the hospital with palpitations, tremors, and dizziness. He was found to be thyrotoxic: T4$>$100pmol/l, TSH $<$0.01 mIU/l. His background includes atrial fibrillation, chronic obstructive pulmonary disease, Type 2 diabetes, hypertension, and high cholesterol. He was taking Amiodarone to manage atrial fibrillation. Amiodarone was then discontinued. 3) An 80-year-old man developed hypothyroidism after being started on Amiodarone. He was known to have ischemic heart disease, atrial fibrillation, and episodes of ventricular tachycardia. Amiodarone was continued as his implantable cardioverter-defibrillator was removed, and he was commenced on thyroxine.
Discussion
Amiodarone is used in some patients to treat arrhythmias. Amiodarone is no longer given as a first-line treatment due to the serious side effects caused by long-term therapy. Common side effects include QT prolongation leading to arrhythmias (Torsades de Pointes), hepatic dysfunction, and thyroid disorders. Amiodarone-induced thyrotoxicosis (AIT) is divided into type 1 and type 2. AIT type 1 occurs in patients with underlying unmasked thyroid disease such as Graves' disease or toxic nodule. Type 2 AIT is due to destructive thyroiditis. Amiodarone-induced hypothyroidism is likely due to the inhibition of thyroid hormone synthesis and is more common in patients with underlying subclinical hypothyroidism.
Conclusion
Patients commencing Amiodarone therapy should have their baseline thyroid function tests checked and then reviewed every six months for early detection of thyroid dysfunction thus avoiding severe episodes of both hypo- and hyperthyroidism.

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P244

Graves' Disease and Muscle Paresis

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Background
Graves' disease is medical condintion requiring early diagnosis and urgent management, which can be challenging due to diverse clinical presentations. The presence of muscle paresis is rare.
Case Presentation
We report a 38-year-old female who presented with muscle paresis, urine and fecal incontinence, because of thyrotoxicosis due to Graves' disease. Clinical manifestation: general weakness, body tremor, tachycardia, palpitations, leg muscle weakness, urinary and fecal incontinence, sweating, weight loss, diarrhea.
Illness history
symptoms of the disease manifestated during the COVID-19 pandemic (March the 2020). As the complaints became more prominent, the patient turned to local hospital Emergency department, thyrotoxicosis was diagnosed (TSH - 0.0 mU/l), treatment with thiamazole 5 mg 3 times/day was prescribed (after a few weeks to reduce to 2 tablets). The patient's well-being improved, but after reducing to 2 tablets, the mentioned complaints reappeared. In June 2020, patient applied to outpatient department to endocrinologist, due to whole body tremor, leg muscle paresis (walking like having cerebral palsy), expressed tachycardia (HR 140 bpm), urinary and fecal incontinence. Patient was reffered and hospitalized to LHSU, Department of Endocrinology.
Investigations
Table No 1.
Ultrasound
Graves' disease.
Thyroid scintigraphy
The total concentration of technetium in the thyroid gland is up to 47.4% (the norm is up to 2.0%). Image of a hyperfunctioning thyroid gland.
Treatment
Thiamazole 40 mg/d, Propranolol 40 mgx3, Prednisolone treatment was given. After euthyroid was reached, total thyroidectomy was performed (Feb 2021) and Levothyroxine 100 mg x1 p/os was prescribed. Patient was referred to an endocrinologist consultation after 1.5 months. Patient had a good clinical recovery

following the treatment of thyrotoxicosis and postoperative hypothyrosis: the symptoms of Graves' disease, muscle paresis, urinary and fecal incontinence regressed. Women became pregnant and delivered healthy newborn in December 2022.

Conclusions

Muscle paresis with urinary and fecal incontinence can be a rare manifestation of Graves' disease, and should be considered in the differential diagnosis when other clinical features of thyrotoxicosis are present.

Table No. 1. Investigations

Result (normal range)	At diagnosis	1 week	3 months	After surgery
Glucose (4,1-5,9 mmol/l)	5,78			
Potassium (3,5-5,1 mmol/l)	3,47	3.67		4.32
Calcium (2,2-2,6 mmol/l)	0, 28	2.54		2.12
Magnesium (0,77-1,03)	0,65	0.76		0.8
Hemoglobine (120-155 g/l)	108	137		
ATPO (0-3,2 kIU/l)	593			
Anti-Tg (0-13,6 kIU/l)	37.8			
TSH (0,5-7,3 mIU/l)	0.03			0.52
FT4 (9-21 pmol/l)	68	48	24	13.2
FT3 (3,3-5,1 pmol/l)	28	14	6	
Anti-TSH (0-4 U/l)	108			

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P245

Large rapidly developing goiter and Acute Leukemia

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Introduction

Many thyroid conditions are associated with the development of a rapidly progressing goiter and should evoke several diagnoses, some of which may be of poor prognosis.

Case-presentation

A 47-year-old female patient with no previous pathological history presented with a large goiter associated with a deteriorated general condition that had been evolving for 3 weeks On examination, she presented with a fever at 39°C, multiple cervical adenopathies of hard and painful consistency, pallor, gingival enlargement, and a painless large goiter of hard consistency, associated with compressive signs: dysphagia and dysphonia. Her biological tests showed: hyperleukocytosis at 77390/mm^3 with 49% blasts, anemia at 7.3 g/dl, and thrombocytopenia at 33000/mm^3. TSH was elevated to 65 mIU/l, FT4 was low at 7.02 pmol/l, LDH was high at 560 IU/ml. Anti-thyroperoxidase and anti-thyroglobulin antibodies were positive at 468 and 566 mIU/ml respectively. The bone marrow aspiration revealed a marrow infiltrated by 59% blasts in favor of acute myeloblastic leukemia type 5 (AML). The karyotype was without abnormality. Immunophenotyping was in favor of Aml. A cervical ultrasound revealed an enlarged thyroid with heterogeneous pseudonodular hypoechoic echostructure associated with multiple cervical adenopathies. Fine needle aspirates (FNA) from the thyroid revealed the presence of benign epithelial cells in both lobes without signs of malignancy. The patient was put on Levothyroxine replacement therapy and treated with Cytarabine and anthracycline chemotherapy. The evolution was marked by a complete remission of her AML and an incomplete regression of her goiter with an improvement of compressive signs.

Discussion

The rapid development of a large goiter in the context of an deteriorated general condition should first evoke: anaplastic cancer, primary thyroid lymphoma, Riedel's Thyroiditis or a secondary thyroid tumor localization. FNA is the key examination in this situation. Our case illustrates the association of AML and Hashimoto's Thyroiditis revealed by a large goiter of rapid evolution. Hashimoto's thyroiditis is associated with a higher risk of developing certain cancers, including leukemia. Various hypotheses have been put forward regarding the underlying pathophysiological mechanisms, including chronic inflammation and its role in oncogenesis. Further studies will be necessary to better elucidate the mechanisms involved.

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P246

Hidden central hypothyroidism in an elderly patient following radioiodine therapy

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Introduction

Thyrotropin deficiency is a rare etiology of hypothyroidism. The diagnosis can be easily confirmed in case of low FT4 level associated with normal or low TSH value. In patients with peripheral hypothyroidism treated by levothyroxine, this biochemical profile become difficult to find. Herein, we describe the case of a patient with peripheral hypothyroidism due to radioiodine therapy in whom the diagnosis of central hypothyroidism was made.

Observation

An 80-year-old patient, type 2 diabetic, followed initially, 15 years ago, for Graves' disease treated by radioiodine then he received levothyroxine for peripheral hypothyroidism. The replacement dose has been decreased gradually from 150µg q.d. to 75µg q.d. before the patient withdrew his treatment 4 months ago. The patient was admitted in our department for intense asthenia and hypoglycemia. He didn't take any medication recently. His renal and hepatic functions were normal. His TSH level was normal for his age at 5 µUI/l although the history of radioiodine therapy. Endocrinological assessment confirmed central hypothyroidism with low FT4 at 7 pmol/l (12-22 pmol/l), corticotropin deficiency with peak cortisol level after Synacthene test at 185 nmol/l and hypogonadotropic hypogonadism with a testosterone level at 0.22 ng/ml. His prolactin level was low at 68 IU/l. Pituitary MRI showed anterior pituitary hypoplasia and pituitary stalk thickening of 4 mm. hydrocortisone replacement therapy was prescribed at the dose of 15 mg q.d. in addition to levothyroxine at the dose of 75 µg q.d.

Conclusion

Decreased levothyroxine requirements in a patient with peripheral hypothyroidism, the persistence or the presence of nonspecific symptoms although normal TSH level should guide clinicians to the diagnosis of thyrotropin deficiency, most frequently associated with other pituitary hormone deficiency.

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P247

Noise Level, Salivary Cortisol Levels and Surgical Team Stress During Thyroidectomy in An Endocrine Surgery Operating Room

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Introduction

Noise in the operating room is an ongoing problem and impacts the outcome of surgery. Noise as stressor can produce a startle reaction and activate fight or flight response of the autonomic and endocrine system. The psychobiology of the stress as assessed by salivary cortisol level is a sensitive measure of allostatic load. In this study, we correlated salivary cortisol levels of the surgical team with noise measurement and also whether the noise in OR subjectively affected the operating team.

Materials & amp; Methods

Prospective observational study conducted in OR of a tertiary referral centre. We recorded the noise or from shifting in to shifting out using digital sound level meter. The operating team – Operating Surgeon (S), Anaesthetist (A), Scrub Nurse (N) and Floor Nurse (F) all gave a salivary sample for measurement of cortisol at the end of the procedure. We had measured baseline salivary cortisol for Surgeons. Questionnaire for assessment of distraction was filled in by the S, A and N at the end of the procedure. Salivary cortisol levels were analysed using SLV-4635(formerly SLV-2930) DRG Instruments GmbH German using ELISA. Statistical analysis was performed using SPSS 22.0.

Results

Total of 37 procedures with 148 Salivary Cortisol samples and 111 responses from S, A and N were analysed. All Patients with benign FNAC were operated (64.9% - Colloid).

Mean TSH levels were 3.5 ± 6.7. Majority had STN (25/37 67.6%). 18 patients (48.6%) underwent open Hemithyroidectomy 10 patients TT and & amp; 8 patients Endoscopic HT and 1 Pt had sistrunk's procedure. The Mean Cortisol levels of S, N, A and F and mean noise levels are provided in the table1. There was significant Correlation between mean noise levels and S& #39;s levels. ($P < 0.05$).

Conclusion

Noise levels were high in the OR during initial phase and closure phase of thyroidectomy. 'S'' was more affected by noise especially during critical phases of Surgery such as RLN dissection. Serum cortisol level were high for S when compared to N, A and F. No studies in Literature regarding noise correlation and Surgeons stress. Noise is distracting and the effect of long term effect on the surgical team needs to be studied.

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P248

Individual experiences and patients' lives: Place of the narrative approach in the therapeutic education plan for thyroid cancer patients

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Objective

To describe the experience of patients with differentiated thyroid carcinoma (DTC) since their diagnosis.

Patients and Methods

Cross-sectional study including 25 patients with DTC who integrated the therapeutic education program (TPE) on DTC at the Nuclear Medicine Center, Sfax, Tunisia. Each participant recounted his or her experience during collective meetings (narrative approach).

Results

Our group was composed of 19 women and 6 men, with an average age of 45.5 ± 15.2 years. The diagnosis was made within the last 3 months in 52%. A thyroid nodule (32%) or adenopathy (32%) were the first warning signs. The diagnosis was announced by the ENT specialist (64%), the treating physician (20%) or the endocrinologist (16%). This experience was satisfactory for 72%. The doctor's communication about the cancerous nature of the CDT was 'vague' for 12%. Also, 16% would have preferred to receive more explicit information. While 68% claimed to have received a clear explanation about the surgical step, 16% would have liked to know more about its objectives. The rest of the treatment protocol (iratherapy, hormone replacement therapy) was fairly well detailed for 80% of the patients. Prior education on the signs of L-thyroxine deficiency/overdose was requested by 40% of participants.

Discussion

The diagnosis of CDT causes an alteration in the patient's identity, which will henceforth be organised around the tale of the disease and the demands of the medical world. The narrative therapy sessions integrated into the ETP programmes would allow access to the patient's subjective experience and lead him/her to reappropriate his/her experience in order to better adhere to the planned therapeutic protocol.

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P249

Papillary Thyroid Carcinoma with Abdominal Desmoid-Type Fibromatosis – A Case Report

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Introduction

Papillary Thyroid Carcinoma is the most frequent malignant tumour of the thyroid gland. It usually progresses slowly and is rarely metastatic. On the other side, fibromatosis are usually benign tumours with infrequent malignant appearances, which affect musculoaponeurotic structures. The aetiology remains unclear, although various possible factors are linked to it such as trauma, genetic predisposition, β-catenin heterozygous mutation, hormone disbalance etc. Even though it benign status, fibramatosis are locally aggressive and can be associated with carcinomas of different kind such as the thyroid. Very few cases are reported in the literature of papillary thyroid cancer with mesenchymal tumours. We present the case of a patient with papillary thyroid cancer in concomitant with a desmoid-type fibromatosis abdominal tumour.

Case Report

The patient, a female of 31 years, came to the Department of Endocrinology after receiving the result of a biopsy. She had undergone total thyroidectomy on February 2020 for a diagnosis of multinodular goitre. The biopsy confirmed papillary thyroid cancer (classical variant) of 2 cm diameter, with capsular and vascular invasion. She was started hormone replacement therapy shortly after the surgery. Upon the arrival of the biopsy, she was planned for radioactive iodine therapy. She received 100 mCi. The patient had a prior surgery, on July 2019. She had an abdominal mass removed. The biopsy of it, supported by immunohistochemistry analysis later, resulted in abdominal desmoids-type fibromatosis. She had no family known history for neither of the diseases. The patient did not receive, apart from surgery, any other therapy for the abdominal tumour. At the time no genetics tests were performed. She is currently under examinations and regular follow-ups with no signs of recurrence.

Conclusions

The presence of both mesenchymal and papillary thyroid malignancy is a rare but present finding. Usually the thyroid is the first to be diagnosed, followed by the mesenchymal tumour, but it depends on the location and aggressive nature of the tumours. Considering the multiple possible factors in fibromatosis, it is important to further explore them in order to choose the better way of treatment and follow up.

Key notes

thyroid carcinoma – fibromatosis – desmoids tumour - biopsy - surgery

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P250

Coexistence of Atypic Parathyroid Tumor and Metastatic Thyroid Papillary Carcinoma

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Introduction

Atypical parathyroid tumour (APT) is a rare cause of primary hyperparathyroidism (PHPT) with a frequency of 1.2-1.3%. APT is a lesion with suspicious clinical and histological features of malignancy which does not completely respect the World Health Organization (WHO) criteria for diagnosis of Parathyroid Carcinoma (PC). There is a well-known association with PHT and medullary thyroid carcinoma for multiple endocrine neoplasia. However, concurrence of thyroid papillary carcinoma and PHPT is rarely defined in the literature. Here we report a case of multifocal thyroid papillary carcinoma accompanying severe hypercalcemia caused by APT.

Case Report

43-year-old female patient was admitted to hospital with the complaint of weakness. Laboratory analyses revealed high serum calcium (14.45 mg/dl) and parathyroid hormone (PTH) (1651 ng/dl) with suppressed phosphorus (2.45 mg/dl). 24 hour urinary calcium excretion was 121 mg/day. The diagnosis was symptomatic PHPT. Bone densitometry showed osteopenia and ultrasonography(USG) was negative for renal calculus. Neck USG revealed a well-circumscribed, 43x27x33 mm, hypoechoic nodular lesion with cystic component close to the left lobe inferior pole, with intense vascularization in the inner structure. Technetium-99m-sestamibi parathyroid imaging showed parathyroid adenoma in the same localization. Also, a 9x8.5x6 mm hypoechoic solid nodule at the right thyroid lobe, containing punctate echogenic foci(ACR-TIRADS-V) and multiple nodules with the size of 5x5 mm (ACR-TIRADS II) and 7x6 mm (ACR-TIRADS IV) were shown by neck USG. Fine needle aspiration biopsy(FNAB) was resulted as Bethesda I for the right thyroid nodule twice. Serum calcitonin level was negative. Parathyroidectomy for symptomatic PHPT and thyroidectomy with frozen examination were planned as surgical procedure. Left lower parathyroid gland was excised. Since frozen examination was suspicious for papillary carcinoma, the patient underwent total thyroidectomy and central neck lymph node dissection. Pathology revealed APT, parathyroid cyst and multifocal classic type papillary microcarcinoma with lymph node metastasis. Serum

calcium, phosphorus and PTH levels returned to normal levels as was 8.6 mg/dl 3.94 mg/dl and 46ng/dl, respectively. The patient was discharged at first day postoperatively without any postoperative complication.
Discussion
Although rarely seen, APT may be the cause of severe hypercalcemia in patients with PHPT especially in those with high PTH and large tumour size. Patients with APT should be strictly followed up as outcome is not known exactly. Thyroid nodules in those undergoing parathyroid surgery should also be evaluated carefully for medullary and non-medullary thyroid carcinoma.

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P251

Dwarfism of the Laron type with normal high affinity serum growth hormone-binding protein

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Introduction
An autosomal recessive illness called the syndrome of familial GH-resistant short stature is characterized by a phenotype that is similar to that of isolated GH deficiency, but with normal or excessive GH production and decreased IGF-I synthesis. When these individuals are treated with GH, neither growth nor a rise in blood somatomedin/IGF-I activity—the mediator of GH's growth-promoting effects—are stimulated. This suggests that the cause of the growth failure is end organ resistance.
Objective
A high-affinity GH-binding protein found in normal serum appears to be identical to the extracellular domain of the GH receptor. In the serum of people with Laron-type dwarfism, it is typically lacking. The goal of this study is to determine the status of a family with Laron-type dwarfism's serum GH binding protein.
Method
An open case study was conducted in a family in which four sisters, who ranged in age from four to sixteen, had the Laron-type dwarfism phenotype. Five unrelated girls with dwarfism of the Laron type and those without endocrine abnormalities served as the control samples. By showing elevated blood OH levels and low serum IGF-I levels on an immunoassay, along with a drop in serum IGF-I levels followed by an increase following GH treatment, Laron-type dwarfism was conclusively proven. Gel chromatography on Sephacryi S-100HR gel electrophoresis following covalent cross-linking to lZ5i-GH, Scatchard analysis of ligand binding, and polyacrylamide gel electrophoresis were used to characterise serum GHbinding proteins.
Results
The GH-binding protein activity in the serum of all family members was similar in affinity. In the same way that normal persons do, calculate the amounts and apparent affinity for OH. The unrelated youngster who had Laron type dwarfism and prior findings of blood OH-binding protein levels in this disorder contrasted this with the very low serum GH binding protein activity in that child.
Conclusions
Since normal cell responsiveness to GH is not required for the production of normal levels of serum GH-BP, it follows that serum GH-BP levels shouldn't be regarded as a quantitative indicator of GH receptor activity or GH bioactivity. When blood GH-binding protein levels are normal, the affected patients may have a unique metabolic abnormality that causes OH resistance and diminished IGF-l synthesis.

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P252

Role of Ayurveda based novel 'Thyroid detoxification program' in the management of hypothyroid patients

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Background
The aim of study was to determine the effectiveness of Thyroid detoxification program therapy in patients of hypothyroidism, attending TATC clinic in Maharashtra. According to the clinical survey from various studies on thyroid disease, it has been estimated that about 32% of people suffer from thyroid diseases in India out of which 10.7 % of people have hypothyroidism. According to health experts, even though hypothyroidism is easy to detect and inexpensive to treat, many patients remain undetected and untreated, thereby impairing their work performance and economic productivity. Common symptoms of hypothyroidism, fatigue, weight gain, constipation, dry skin, hoarseness and anemia (usually normochromic and normocytic but occasionally macrocytic). Levothyroxine, synthetic T4 hormone has always been considered as the mainstay of treatment in hypothyroidism. However even after normalization of TSH and T4 levels after LT4 treatment, many patients have persistent complaints. Thus there is an emerging need of an alternative therapy aiming at managing thyroid imbalance along with improvement in clinical symptoms.
Methods
This was a retrospective study conducted from June 21 to April 22, wherein we identified the data of 32 female patients suffering from hypothyroidism who had attended the outpatient departments of TATC clinics across Maharashtra. The data of patients, who had been administered with min of 2 detox procedures and oral Ayurvedic medication over a span of 16 weeks, considered for the study.
Results
Medical records of 32 patients were analyzed. At the end of the therapy, there was reduction in symptoms of hypothyroidism like palpitations, mood swings, fatigue, dry skin, joint pain, muscle crampsstiffness, indigestion, depression, anxiety. The alleviation of symptoms started in average one month from the commencement of treatment and patients were asymptomatic at the end of 16 weeks. There was reduction in standard of care thyroxine hormone for 100% subjects in four months. Average baseline levels of TSH in patients was found to be 9.49 uIU/ml. After two months of treatment, it was found that the TSH levels reduced significantly to 5.77 uIU/ml. The average duration required by the patients to reduce the dose was four months. Slight increase in TSH levels observed in further visits but it was not significant. Thus it indicates that intended therapy not only has a potential effect in maintaining normal thyroid hormone levels but it also treats root cause of thyroid imbalance which is evident by the reduced dose of medication and improved quality of life of patients.

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P253

Interplay between thyroid, amiodarone and heart - case presentation

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Background
Amiodarone is a commonly used antiarrhythmic drug, but because of its abundance with iodine and a direct toxic effect on the thyroid, it can have side effects like hypo- and hyperthyroidism. There are two types of amiodarone-induced thyrotoxicosis (AIT). We present a case which demonstrates the importance of timely diagnosis and appropriate treatment of amiodarone-induced thyrotoxicosis in patients with serious cardiac comorbidities.
Case presentation
A 74-year-old male with a history of a thyroid checkup in 2019 after accidental finding on CT, when neck ultrasound (US) and scintigraphy were performed (ultrasound showed a multinodular goiter; scintigraphy showed several warm nodules), hypertension, paroxysmal atrial fibrillation, implanted mechanical aortic valve because of aortic regurgitation, left ventricular hypertrophy, and reduced ejection fraction, was referred to our clinic because of hyperthyroidism. Four months prior to this visit amiodarone was discontinued by his cardiologist after five years of use. At the time of amiodarone discontinuation the patient had a thyroid stimulating hormone (TSH) level below the lower reference limit and no hypermetabolic symptoms. No thyrostatic treatment was initiated nor was he referred to an endocrinologist. The patient developed symptoms of hyperthyroidism two months later; TSH was suppressed. His primary care physician started him on 10 mg of thiamazole daily. After two more months, the patient's state worsened. He was referred to an otorhinolaryngologist who advised the patient to visit our clinic. US was repeated, confirming the presence of multinodular goiter, no signs of gland destruction were present, and vascularisation was neither increased nor absent. At that point urgent restoration of stable clinical state was necessary because the patient had cardiac decompensation and overt hyperthyroidism with suppressed TSH and high free thyroxine (FT4) level, as well as prolonged prothrombin time due to coumarin use. After cardiac recompensation, normalization of the coagulogram, and reduction of the FT4 level under full thiamazole dose (which stayed slightly above the upper reference limit), thyroidectomy was performed. Significant clinical and laboratory improvement followed.
Conclusions
AIT has been associated with increased morbidity and mortality, especially in older patients with impaired left ventricular function. The importance of regular monitoring of thyroid status in amiodarone users and rapid recovery and stable maintenance of euthyroidism when necessary, should be emphasized to both endocrinologists and non-endocrinologists.

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P254

Endocrine adverse events associated with immune checkpoint inhibitors - A case series

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Background
Immune checkpoint inhibitors (ICIs) are a novel group of drugs, used for treatment of various types of malignancies. The receptors cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein-1 (PD-1) or its ligand (PDL-1) are targeted by those inhibitors. They are associated with immune-related adverse events (irAEs). Endocrinopathies are the most frequent irAEs with a prevalence of approximately 10%.
Case study
We retrospectively described a series of patients with endocrine complications caused by ICIs. Out of 24 patients treated with single or combination therapies, 18 patients developed endocrinopathies. The median age at diagnosis was 59 years and onset of endocrine dysfunction occurred within a median of 12 weeks of first ICIs exposure. Our case reports uncover a broad spectrum of ICI-induced endocrinopathies: 13 patients with thyroid dysfunction, 6 patients with hypopituitarism and one with primary adrenal deficiency. Polyglandular endocrine complications were described in two patients. Clinical presentation varied from asymptomatic patients to life-threatening symptoms. Thyroid disease ranged from subacute thyroiditis to subclinical hypothyroidism or hyperthyroidism, overt thyrotoxicosis and even myxedema. The most frequent ICIs used were PD-1 and PDL-1 inhibitors. Three patients had previous tyrosine-kinase inhibitor (Sunitib)-induced hypothyroidism and four patients had already autoimmune thyroiditis. We encountered six patients with hypophysitis, from which four presented isolated deficiencies (2 with secondary adrenal deficiency and 2 with secondary hypogonadism) and two had multiple deficiencies (one with panhypopituitarism and one with secondary hypothyroidism and adrenal deficiency). Five patients were treated with anti PD-1 or PDL-1 monoclonal antibodies (mAb) and only one with anti CTLA-4 mAb (Ipilimumab).
Conclusions
The most frequent ICIs induced endocrinopathy is thyroid dysfunction, followed by hypophysitis. Primary adrenal insufficiency, although a rare complication, was also reported. In most of our cases, they were irreversible and required hormone replacement. Anti-PD-1 and anti-PDL-1 mAb were frequently associated with thyroid disease. Several studies indicate that CTLA-4 inhibitor is most related to hypophysitis (1), but in our series, we had a single patient in treatment with Ipilimumab, being the one with panhypopituitarism. Therefore, physicians should be aware of ICIs induced-endocrine irAEs in order to properly address, diagnose and treat them at onset and follow-up.
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P255

Two-year case series of a thyroid consultation at a hospital unit

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This paper aims to describe the followed population in the consultation, through a retrospective study in a hospital unit. This retrospective study was carried out during February 2020 to February 2022, and analyses the clinical processes of the patients that were followed in this consultation, and later analysing the data using Microsoft Excel® Over these two years, 395 patients were observed. These patients age average 61 years old, ranging from 17 to 93 years of age. Most patients (83.80%) are female. The most prevalent pathology was thyroid nodule (20.60%), followed by multinodular goiter (20.20%), multinodular thyroid (19.20%), hypothyroidism (14.00%), hyperthyroidism (9.80%), autoimmune thyroiditis (6.40%). The least frequently observed pathologies were thyroid neoplasia (0.40%), myxedema (0.60%), goiter (1.80%), Hashimoto's thyroiditis (2.00%), substernal goiter (2.40%) and Graves' disease (2.60%). 51.14% of the patients underwent aspiration puncture of the nodule. In the majority (87.62%) this nodule was Bethesda category I/II. During the analyzed period, 27.34% of the patients were discharged, 2.03% were referred to the endocrinology consultation at the central reference hospital and 2.03% to the surgery consultation. Thyroid pathology is a multifactorial disease, that mainly affects women and elderly people. There are many diseases that affect the thyroid. These diseases afflictions range from functional deficits to autoimmune pathologies. The most prevalent is the presence of nodules, in patients with or without goiter. This particular result goes against what was observed in our previous statistical work. Despite this, and since biopsies were carried out in most patients, it is important to note that in this specific sample, only two patients were identified with neoplasia.

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P256

Non-secreting pheochromocytoma or adrenal metastasis of medullary thyroid cancer? When the differential diagnosis is difficult

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Introduction
Medullary thyroid cancer (MTC) accounts for 5-10% of thyroid cancers.25% of cases may be hereditary related to multiple endocrine neoplasia type 2 A (MEN2A) and associated with pheochromocytoma. Metastases from CMT are preferentially lymph node chains. However, other localizations are possible such as adrenal metastases which remain exceptional.
Observation
We report the case of a 35-year-old patient with CMT for which he underwent thyroidectomy and lymph node dissection classified as PT2N0Mx. A search for an associated pheochromocytoma and primary hyperparathyroidism in the context of MEN2A, metoxylate assay and a phosphocalcic assessment were normal. A thoracic-abdominal-pelvic CT scan showed a right adrenal nodule measuring 18x25 mm with a spontaneous density of 31 HU, an absolute washout of 25% and a relative washout of 16% in favour of malignancy. No other secondary locations were found. In order to assess the secretory or non-secretory nature of the nodule, the biological tests for hypersecretion of glucocorticoids, catecholamines and mineralocorticoids were normal. A MIBG scan was performed, showing a right adrenal neuroectodermal process. The patient underwent surgery and the pathological study came back in favour of a non-secreting pheochromocytoma.
Discussion
Two diagnostic hypotheses presented themselves:
- Non-functional pheochromocytoma which can be observed in 14-55% of cases. Although in the case of MEN2A, the pheochromocytoma is most often bilateral.
- The second is a metastasis of medullary thyroid carcinoma, which remains exceptional.

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P257

Fear of recurrence of differentiated thyroid cancer in patients in remission

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Objective
to evaluate the fear of recurrence of differentiated thyroid cancer (DTC) in patients in complete remission.
Patients and Methods
Cross-sectional study of 41 patients in complete remission after treatment of DTC, followed up at the Nuclear Medicine Centre of Sfax, Tunisia. The evaluation was based on the administration of a shortened version of the Fear of Cancer Recurrence Inventory (FCRI-SF) to all patients (maximum score 36 points)

Results
The mean age of the patients interviewed was 45.4 ± 13.4 years with a predominance of females (92.7%). The majority had papillary carcinoma (87.8%), more rarely vesicular carcinoma (12.2%). Initial metastases were reported in 9.8% of cases. Thus, 21.9% of carcinomas were classified as high risk. The mean cumulative ablative dose of iodine-131 was 265.9 ± 197 mCi. The mean disease-free survival was 5.1 ± 3.9 years. The FCRI score was 10.9 ± 8 points with extremes ranging from 0 to 26 points. A significant fear of recurrence was noted in 10.8% of the patients surveyed. Concerns about DTC relapse were ' unclear ' for 18.9%. The majority of patients were no longer worried about the relapse (70.3%). Factors associated with a significant fear of recurrence were vesicular type (OR = 0.16; $P = 0.028$) and histological evidence of angioinvasion (OR = 0.12; $P = 0.022$).
Discussion
The fear of recurrence in DTC is significantly lower than that observed in other cancers (breast = 60%, colorectal = 38%). A collaborative therapeutic approach including the patient and his relatives helps to reassure patients about the good prognosis of DTC.

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P258

Widely invasive follicular thyroid carcinoma. A case report

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Follicular thyroid carcinoma (FTC) is the second most common type of thyroid cancer, making up about 10 to up to 15% of all thyroid cancers. It is called a 'well differentiated' thyroid carcinoma, like papillary thyroid cancer, but it is typically more aggressive than this. We report the case of a 75-year-old man with personal history of Type 1 Diabetes since he was 25 years old, with severe nonproliferative diabetic retinopathy (blindness) and multinodular goiter. In 2020, a hypoechoic thyroid nodule of 45 mm with intranodular hypervascularity (TIRADS 4) was detected, but the patient refused to perform a fine-needle aspiration biopsy because of COVID-19 pandemic. He didn't come to Endocrinology appointments until 2022, when we performed a new thyroid ultrasound. The TIRADS-4 thyroid nodule had grown up 7 mm and another nodules had appeared. In addition, the patient reported compressive symptoms, so we offered him a total thyroidectomy, but he refused. Several months later, the patient reported 10 kg weight loss and dysphagia, so he accepted thyroidectomy and we ordered a computed tomography (TC) and a general surgeon consult. TC shown a severe tracheal compression and the patient developed in a few days dyspnea and hoarseness. He was admitted to the hospital and a bronchoscopy was performed, revealing tracheal compression by extraluminal mass on the left lobe of the thyroid. Tracheal lumen was narrowed by 40%, so he was admitted to the intensive care unit (ICU) and, some days after that, a total thyroidectomy was performed. The microscopic examination of the surgical piece established the diagnosis of a widely invasive FTC (angioinvasion, extrathyroidal extension and lymph node metastasis) T4aN1Mx (stage IV AJCC 8th edition). During hospitalization the patient received nasogastric tube feeding. It was difficult for him to express his desires and to communicate with others because of his blindness and the tracheostomy, but due to the speech therapist work he returned to talk some weeks later. Two months after surgery, serum thyroglobulin level was 6,5 ng/ml and antithyroglobulin antibodies were negative. At this time our patient is waiting to radioactive iodine therapy. Most FTCs are slow growing and are associated with a very favorable prognosis. Despite of that, we must pay attention to a very rapid growth of a thyroid nodule because it should raise the suspicion of thyroid carcinoma, especially in patients affected by multiple chronic diseases.

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P259

Male with Graves Disease and Primary Thyroid Cancer in the Thyroglossal Cyst

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Introduction
The malignancy of the thyroglossal duct cyst is infrequent, 0.7 to 1% of the thyroglossal duct cysts, predominantly in women and euthyroid subjects, some associated with Hashimoto's Thyroiditis.
Clinical case
Male, 42 years old, with a 5-year history of a large anterior cervical tumor, diagnosed with Graves' disease and thyroid orbitopathy. Cervical ultrasound reports right submandibular region mixed tumor mass 36 x30. mm with nonspecific lateral cervical lymph nodes and multiple mixed oval images, well-defined borders, less than 13 mm in diameter. The ophthalmological evaluation reports moderate quiescent orbitopathy. He received treatment with high doses of methimazole and lithium carbonate for severe hyperthyroidism with difficult stabilization. Sistrunk surgery and total thyroidectomy was performed. Histology reports papillary thyroid carcinoma on a thyroglossal duct cyst, 1, 5 cm, without evidence of thyroid neoplasia.
Discussion
In the literature reviewed, no association was reported with primary papillary thyroid carcinoma in a thyroglossal cyst and Graves' disease. Due to the low frequency of papillary thyroid carcinoma in the thyroglossal duct, a single algorithm has not been reached for its treatment and follow-up, it must be approached by a multidisciplinary team based on the current guidelines for differentiated thyroid cancer, which coincide that Sitrunk surgery and total thyroidectomy is the most appropriate initial treatment.

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P478

Mouse model of Graves' ophthalmopathy induced by the immunization with TSHR A and IGF-1Rα subunit gene

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Background
The study aimed to establish a mouse model of Graves' disease (GD) with Graves' ophthalmopathy (GO; GD + GO) that can represent the clinical disease characteristics.
Methods
A eukaryotic expression plasmid of insulin-like growth factor 1 receptor (IGF-1R) α subunit (pcDNA3.1/IGF-1Rα) and a thyrotropin receptor (TSHR) A subunit plasmid (pcDNA3.1/TSHR-289) were injected in female BALB/c mice to induce a GD + GO model. Grouping was performed according to the frequency of injection (2- to 4-week intervals) and type of injected plasmids: T: pcDNA3.1/TSHR-289(+), I:pcDNA3.1/IGF-1Rα(+), or co-injection T + I: pcDNA3.1/TSHR-289(+) and pcDNA3.1/IGF-1Rα(+). Serum TSH, T4, TSAb, body weight, and blood glucose levels were evaluated. Thyroid $^{99m}TcO_4^-$ imaging and retrobulbar magnetic resonance imaging (MRI) were performed, and bilateral eye muscle volumes were measured. Immunohistochemistry and hematoxylin-eosin (HE) staining of relevant tissues were performed.
Results
A total of 60% of mice (3/5, one mouse died) in the pcDNA3.1/TSHR-289(+) group developed GD + GO. In the pcDNA3.1/TSHR-289(+) and pcDNA3.1/IGF-1Rα (+) groups, 83.3% of mice (5/6) developed GD + GO. Mice in the pcDNA3.1/IGF-1Rα (+) group did not develop GD. Compared with the control group, serum T4, TSAb, and TSBAb of the mice in the GD + GO model groups were increased to varying degrees ($P < 0.05$), and serum TSH and body weight were significantly lower compared to the control group ($P < 0.05$). The blood glucose of the mice in each group had no significant difference. The thyroid uptake capacity of $^{99m}TcO_4^-$ and the volume of eye muscle of mice in the GD + GO group were significantly higher compared to the control group ($P < 0.05$). The thyroid, retrobulbar muscles, heart, and liver of these mice showed varying inflammatory infiltration, interstitial muscle edema, and hepatic vein congestion. The severity of GD + GO in the co-injection group was not related to injection frequency; however, GD and ocular signs in co-injection mice were more severe compared to the pcDNA3.1/TSHR-289(+) group.
Conclusions
We successfully induced a GD + GO mouse model by a repeated co-injection of pcDNA3.1/IGF-1Rα and pcDNA3.1/TSHR-289 plasmids. Injection of pcDNA3.1/IGF-1Rα alone failed to induce GD. Co-injection of two plasmids induced more severe GD + GO than pcDNA3.1/TSHR-289(+) alone.
Keywords
Graves' disease, Graves' ophthalmopathy, IGF-1R, TSHR

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P479

Clinical significance of IgG4 serum concentration in Graves Disease – a pilot study

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Background
Immuglobulin 4 (IgG4) is the least common subtype of Immoglobulin G. However due to its unique characteristic it has been the focal point of many research projects, which eventualy led to the discovery of the sytemic fibro-inflammatory disorder called IgG4-Related Disease. The potential role of IgG4 in the pathogenesis of autoimmune thyroid diseases has been also suggested. However, the amount of evidence is still limited, especially in Graves Disease (GD).
Objective
In this study we aimed to assess the prevalence of patients with high IgG4 GD and the corelations between IgG4 and other clinical, ultrasounographic and biochemical parameters.
Methods
60 patients with GD were recruited. The study group was divided into 3 subgroups: Group 1 – hyperthyroid patients with newly diagnosed GD ($n=29$); Group 2 – euthyroid patients with GD after antythyroid treatment ($n=19$); Group 3 – patients with moderate to sever Graves Orbitopathy (GO) ($n=12$). Only patients who had not been previously treated with thyroidectomy or radioiodine were included in the study. All patients underwent a detailed laboratory assessment and ultrasonographic evaluation. IgG4 serum concentration was evaluated with the ELISA method. High IgG4 GD was defined as IgG4 serum >135 mg/dl.
Results
The prevalence of high IgG4 GD was low among GD patients without orbitopathy (4%) and substantially higher in patients with GO (33%). IgG4 serum concentration was higher in GO group than in the hyperthyroid and euthyroid GD groups (87.9 [61.55; 143.78] vs 31.4 [23.7; 41.7] mg/dl, $P<0.001$ and vs 30.1 [26.95; 79.6] mg/dl, $P=0.015$, respectively). There was no difference in IgG4 levels between the hyperthyroid and euthyroid GD groups, despite massive differences in anti-TSH receptor antibodies (TRAb) (29 [12.92; 6.38] vs 1.93 [0.78; 3.46] $P<0.001$), anti-thyroperoxidase antibodies (TPOAb) (274 [62; 522.75] vs 37 [21.5; 122.5] $P=0.005$). There were no statistically significant correlations between IgG4 levels and thyroid stimulating hormone (TSH), free thyroid hormones, TRAb, TPOAb and anti-thyroglobulin antibodies (TgAb) levels nor with thyroid volume, thyroid echogenicity, intrathyroidal blood flow. Patients with multiple thyroid nodules ($>=3$) had significantly lower IgG4 levels than those with <3 nodules (41.35 [29.5; 91.93 vs 25.7 [23.8; 26.3] mg/dl, $P=0.026$).
Conclusions
Our results suggest that IgG4 serum concentration is associated with the occurence of Graves Orbitopathy. The IgG4 serum concentration seems to be unrelated to TRAb, TPOAb or TgAb levels. Further studies, especially with a longitudinal design, are needed to determine the influence of IgG4 levels on the treatment outcomes and prognosis of GD patients.

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P480

A Prospective Comparitive Study on Cardiovascular Dysfunction and its Reversal After Treatment in Patients with Graves and Toxic Multi Nodular Goitre

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Cardiovascular dysfunction (CVD) is a well recognized complication in patients with hyperthyroidism and is the major cause of mortality. To date there has been no studies which had clearly evaluated the CVD and its recovery pattern between patients with Graves and Toxic multi nodular goitre(TMNG). Hence we intended to compare treatment outcomes in patients with Graves and TMNG. Patients with hyperthyroidism were grouped into, **Group 1** [$n=133$, age <60 years, proven Graves, **Group 2**[$n=64$, age <60 years, proven TMNG] were evaluated with 2D Echocardiography, at the time of diagnosis(Point A), after achieving euthyroidism(Point B) with anti-thyroid drugs and 6 months after achieving euthyroidism (Point C). 40 patients(**Group 3**), age <60 years, with nontoxic benign thyroid nodules served as controls. All groups were age and sex matched. At point A, CVD was evident in 88/133(66.2%) in Group 1 and 39/64(60.9%) in Group 2. At Point B improvement in CVD occurred in 55/88(62.5%) in Group 1and 22/39(56.4%) in Group 2. At Point C dramatic improvement in CVD occurred in 82/88(93.1%) in Group 1, whereas only 28/39(71.7%) improved in Group 2. Though incidence of CVD was more in group I the improvements in dysfunction parameters were more pronounced in group I after treatment. At Point C there was a significant decrease in all the cardiac dysfunction parameters in Group 1 whereas the same was not observed in Group 2 patients (Table1). Cardiac dysfunction parameters improved significantly in patients with Graves after treatment than in patients with Toxic MNG and hence those patients with Toxic MNGs should be treated more cautiously owing to the increased morbidity due to cardiovascular dysfunction.

TABLE 1 IVS-Interventricular septum LV-left ventricle

Variables	Group 1	Group 2	p value
LV End diastolic dimension(mm)	40.72±4.07	41.95±5.21	**.002**
LV End systolic dimension (mm)	26.11±3.06	28.18±4.1	**.01**
LV End diastolic volume (ml)	68.86±12.07	75.09±9.41	**.03**
LV End systolic volume (ml)	31.09±7.34	33.12±6.73	**.04**
LV ejection fraction	64.08±4.11	61.54±3.83	**.01**
IVS diastolic thickness	9.09±1.06	9.9±1.51	.14
Posterior wall thickness	9.14±1.7	9.38±1.4	.57
pulmonary hypertension	23.05±2.3	24.08±2.35	**.07**

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P481

CytoFoam core device: an innovative support for immunocytochemical assessment in cytologically indeterminate thyroid nodules

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Background
Fine needle aspiration (FNA) is the procedure of choice in the evaluation of thyroid nodules. Nodules with indeterminate cytological categories, Bethesda III and IV, pose challenges in clinical practice and are frequently submitted to diagnostic surgery. Immunohistochemistry provides complementary information to cytological findings but its reliable use on FNA samples is hampered by technical problems. CytoFoam Core (CFCS), an absorbent foam device inserted into the needle hub, collects the cytological sample aspirated during FNA and may overcome these difficulties because a formalin-fixed and paraffin-embedded specimen, well suitable for ancillary techniques, is provided.
Aim of the study
To assess diagnostic efficacy of CFCS, compared to traditional cytology, in re-evaluating thyroid nodules classified as Bethesda III. Post-surgical histology was used as reference standard.
Method
Retrospective study on 89 patients with a first indeterminate cytological report referred to Department of Endocrinology of Regina Apostolorum Hospital (Albano L. Rome, Italy) for a second FNA. FNA was performed, after at least one month, under ultrasound guidance with a 23G needle according to the established procedure. Both traditional cytological (TC) smears and a single-pass CFCS specimen were obtained for each patient. On CFCS samples immunocytochemical staining for Galectin-3, HBME-1, and CK-19 were performed. Fifty-one patients underwent surgery and their histological diagnoses were blindly compared to the TC and CFCS reports. Four parameters were evaluated: inadequacy rate, rate of persistent indeterminate (Bethesda III and IV) reports, rate of malignancy in persistently indeterminate nodules, and rate of cancer in lesions cytologically classified as malignant.
Results
Non-diagnostic samples were 6 (11.8%) in TC vs 3 (5.9%) in CFCS ($P=0.4$). Persistent indeterminate samples were 31 (60.8%) in TC vs 19 (37.2%) in CFCS ($P=0.01$). Rate of malignancy in persistently indeterminate nodules was 8/19 (42.1%) in CFCS vs 9/31 (29%) in TC group ($P=0.3$). Nine/51 (17.6%) samples were reclassified as benign by TC vs 21/51 (41.2%) samples by CFCS ($P<0.01$). All benign nodules were confirmed as benign at post-surgical evaluation. Five/51 (9.8%) samples were classified as suspicious for malignancy/malignant in TC group against 8/51 (15.7%) samples in CFCS ($P=0.5$). Post-surgical evaluation confirmed malignancy in all these cases.
Conclusion
CFCS significantly improved diagnostic accuracy of TC in repeat FNA assessment of cytologically indeterminate nodules. CFCS increased the conclusive diagnosis rate and decreased the number of cytologically indeterminate cases.

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P482

Sonographic and clinicopathological differences between non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) and minimally invasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC)

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Background
Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is a newly described indolent thyroid tumor with well-defined histopathological diagnostic criteria. Even though the histopathologic features and diagnostic criteria for NIFTP are well-established, preoperative diagnosis using sonographic or fine needle aspiration findings has yet to be confirmed. The aim of this study is to compare the clinical, sonographic, and cytological characteristics of NIFTP with minimally invasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC).
Methods
We examined the records of 73 patients who underwent thyroid surgery at Hacettepe University Hospital between 2016 and 2022 with a postoperative diagnosis of NIFTP or EFVPTC. A detailed analysis of patients' medical charts and pathology reports was used to analyze clinicopathological features retrospectively.
Results
The 73-case cohort consisted of 42 NIFTP and 31 IFVPTC cases (median age 54 years, 47 (64 %) women). NIFTP group was consisted of more female sex subjects ($P<0{,}001$). The ultrasound findings for NIFTP and minimally invasive EFVPTC typically demonstrated a circumscribed oval/round nodule with a hypoechoic rim. Presence of halo in nodules was significantly more prevalent in the EFVPTC group ($P<0.001$). 47.6% of the nodules in NIFTP were solid-cystic, 42% solid, and 9.5% cystic. These ratios were similar in EFVPTC (35.5%, 48.4%, and 16.1%, respectively). There were no differences in microcalcification in nodules ($P=0.06$). Metastatic lymph node(s) was found in 8 cases of EFVPTC but none in NIFTP ($P<0.001$). In NIFTP, the prevalence of nodules being TIRADS 2, 3, 4, and 5 was 21,4%, 23,8%, 45,2%, 7,1%, respectively. EFVPTC group had more TIRADS-5 nodules ($P<0{,}01$). The NIFTP and EFVPTC groups showed benign features, with a majority of the patients categorized as Bethesda category III (39,5 % and 25.8%, respectively) ($P<0.02$) or IV (28,5% and 30.2%, respectively). Lobectomy has been performed in only 9% (4/42) of NIFTP cases. Total thyroidectomy was the preferred surgical method in remaining NIFTP and all EFVPTC cases. CK19 staining of nodules in EFVPTC was more prevalent ($P<0.001$). TNM stages of the groups were similar, too. The rates of postoperative hypoparathyroidism were also comparable ($P=0.32$). During follow-up, no recurrence or metastasis was observed in any case.
Conclusions
These results demonstrate that NIFTP and EFVPTC are clinically and sonographically similar, despite being pathologically recognized by well-defined criteria. In our study, the presence of peripheral halo, irregular margins, and CK 19 staining in pathology were more common in EFVPTC, which may support the preoperative diagnosis.

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P483

Cytokine levels and the effect of the Covid-19 pandemic on the course of Graves' disease under antithyroid treatment

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Objective
Graves' disease (GD) occurs as a result of genetic and environmental factors that trigger autoimmunity. Some pro-inflammatory cytokines have already been linked to an increased susceptibility of developing GD. Recently, it has been reported that Covid-19 infection and SARS-CoV-2 vaccination trigger the emergence of new GD cases or disease recurrence as environmental factors due to the pandemic. However, there is no data in the literature reporting the effects of this pandemic in GD patients who are newly diagnosed and followed up under medical treatment. Here, we aimed to report the effect of the pandemic (vaccination/infection) on the prognosis while examining the cytokine level changes in patients with newly diagnosed GD and receiving treatment.
Material and method
Between December 2019 and June 2021, 41 newly diagnosed GD patients (30 Female/11 Male) were included in the study. The control group consisted of 38 age and gender matched healthy individuals. Cytokine (TNF-alpha, IFN-gamma, IL-10, IL-13, IL-17, IL-22, IL-23 and IP-10) levels were measured by ELISA method from serum samples at baseline and at 6th and 12th months of antithyroid drug (ATD) treatment.
Results
The mean age of the patients was 41.02 ± 11.6 years. Baseline serum TNF-alpha ($P=0.11$) and IP-10 ($P=0.003$) levels were higher in GD patients than in controls. As seen in the Table below, serum IFN-gamma, IL-13, IL-17, and IP-10 levels were significantly decreased compared to baseline under ATD treatment. In contrast, other cytokine levels did not differ statistically with treatment. Of the patients who had both clinical and hormonal control under ATD treatment, 90% ($n=37$) were vaccinated, and 41% ($n=17$) had Covid-19 infection. In both cases, there was no increase in either ATD doses or TSH receptor antibody levels.
Conclusions
The significant decrease in IP-10, IFN-gamma, IL-13 and IL-17 levels with antithyroid treatment showed that these cytokines may play a role in GD in our population. In addition, it was observed that neither Covid-19 infection nor vaccination adversely affected disease activity in GD patients who were newly diagnosed and whose disease was controlled by ATD treatment.

TABLE 1 Cytokines that change significantly with treatment in GD patients

Cytokines	Baseline	At 6th months of ATD treatment	At 12th months of ATD treatment	p
IFN-gamma (pg/ml)	8.82 (3.64-34.40)	8.57 (3.41-21,12)	7.57(4.56-33.46)	**0.004**
IL-13 (pg/ml)	26.13 (18.12-56.79)	22.68 (18.18-43.26)	25.15 (17.60-43.72)	**0.028**
IL-17 (pg/ml)	28.99±11.74	27.08±11.06	24.60±10.80	**0.001**
IP-10 (pg/ml)	61.27±12.13	50.81±12.33	45.40±17.67	**0.016**

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Normative Values for the Hypoparathyroidism Patient Questionnaire (HPQ28) in the General German Population

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Introduction
Patients with hypoparathyroidism (hypoPT) suffer from a number of complaints and reduced quality of life (QoL) besides having serum values for disease-specific parameters in the target range. To be able to quantify symptoms in hypoPT patients we lately developed a disease-specific questionnaire, the Hypoparathyroidism patient questionnaire with 28 items (HPQ28). The aim of this study was to present normative values for the HPQ28.
Methods
A representative sample of the German general population ($n=2509$) was tested with the HPQ28. The HPQ28 consists of five scales and three single items with 28 items in total. The five scales indicate different areas of complaints: Pain and cramps (PaC) including 5 items, neurovegetative symptoms (NVS) including 5 items, loss of vitality (Vit) including 6 items, depression and anxiety (DaA) including 5 items, gastro-intestinal symptoms (GIS) including 2 items and two control items for depression. Three items were not attributable to any of the five scales.
Results
Mean age of the healthy population sample was 50 ±18 years. Men (49%) and women (51%) were equally distributed. To investigate influence of age and gender on symptoms and QoL participants were organized into seven age classes. All scales and single items, except for GiS, were affected by age in male and females ($P<0.001$). In addition, all scales and single items were affected by gender ($P<0.001$). Hence, in the general German population females report highly significant more complaints ($P<0.001$) on every scale and single item of the HPQ28 compared to men. Symptoms and complaints also increase in older subjects. Regression analyses proved a linear trend in the different scores. Percentile rank norms are given for all scores and items.
Conclusion
Analysis in the German population sample revealed gender and age dependency of scores and items of the HPQ28. The regression coefficients now allow the

calculation of expected mean scores for each age and gender distribution of any sample of patients.

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P485

Graves' Disease in A Patient with Thyroid Hormone Resistance

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Introduction
While Graves' disease is a common cause of thyrotoxicosis, tyroid hormone resistance (THR) is a rare cause of high thyroid hormones. Coexistence of Graves' disease and THR which can cause quite a lot of difficulties in diagnosis and treatment was reported very rarely in the literature. Here, we report a patient with THR and Graves' disease in whom remission was achieved with medical therapy.
Case
A 38-year-old woman applied to our clinic with sweating and palpitation. Familial history revealed THR in her sister. Her body temperature was 37.2°C, heart rate was 120 beats/minute, respiratory rate was 18 breaths/minute and blood pressure was 120/70 mmHg. In laboratory examinations, thyroid stimulating hormone (TSH) was 0.018 mU/l (0.55-4.78 mU/l), free T4 was 2.64 ng/dl (0.89-1.7 ng/dl), free T3 was 9.05 ng/l (2.3-4.2 ng/l), anti-thyroglobulin and anti-thyroid peroxidase were negative, TSH receptor antibody (TRAB) was positive. Thyroid ultrasonography revealed chronic thyroiditis and technetium 99m scintigraphy showed heterogeneous activity. When laboratory results were examined retrospectively, we saw that in previous 3 years, her TSH, free T4 and free T3 ranged between 0.84-1.75 mU/l, 1.87-2.12 ng/dl and 4.77-5.86 ng/l, respectively. Thus, the patient had the lowest TSH value and highest free thyroid hormones in her life when she applied. With the current laboratory results and imaging findings, Graves' disease was diagnosed. Methimazole and propranolol treatment was started. Methimazole was switched to propylthiouracil due to the development of skin rash. Owing to family history and her previous thyroid hormone profile, THRB gene mutation analysis was requested from the patient. Heterozygous c.1001T>C mutation was detected. Under treatment, her symptoms resolved, TSH returned to normal, free T3 and T4 were followed as close to the upper limit or slightly elevated. The patient's propylthiouracil medication therapy was discontinued after 18 months. At the time of discontinuation her TSH was 0.96 mU/l, free T3 was 6.05 ng/l, free T4 was 1.98 ng/dl, TRAB was negative. At the last visit, 2 years had passed since drug discontinuation and her serum TSH was 0.51 mU/l, free T3 was 4.86 ng/l and free T4 was 1,50 ng/dl.
Discussion
Treatment with anti-thyroid drugs remains the primary choice for Graves' hyperthyroidism complicated by THR. The optimal treatment is to normalize TSH while keeping free thyroid hormones slightly higher than the upper limit. Iodine therapy and surgery are not generally recommended, since they may induce severe hypothyroidism.

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P486

History of Goiter in The Mother is Associated with Thyroid Volume, TSH and Thyroid Heterpogeneity in Women at Midlife

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Family history of thyroid disease (Karger 2010) and family history of goiter (Singer 2011, Knudsen 2003, Gebremichael 2020) were found to be associated with risk of goiter though some did not observe this association (Phitayakorn 2006). On participants of the Isparta Menopause and Health (IMH) Study, we measured TSH ($n=1099$) and thyroid sonographic parameters ($n=994$) including TV, thyroid nodularity (TN) and heterogeneity (TH). Health related factors and history of goiter in the mother were evaluated through a questionnaire. History of maternal goiter was positive if participant recalled the existence of goiter in her mother and negative otherwise. Univariate and multivariate ordinal (for TV and TSH) and binary (for TH, TN) logistic regression was performed to evaluate the significance of history of maternal goiter as a predictor of TSH, TV, TN and TH. Stepwise model selection algorythm was applied. MVA was performed in 2 steps and response variables were also evaluated as predictors for each other in the second step. The age range of IMH study participants was 44-61. Median TV (interquartile range) was 13 (10, 18.75) ml. Median TSH (interquartile range) was 1.1858 (0.7527, 1.9576) uIU/ml. At least one thyroid nodule was present in 540 (54.44) women. Sonographic heterogeneity was present in 347 (34.98) women. $n=170$ (15.47) women had history of goiter in their mother. In univariate analysis, history of maternal goiter tended to predict increased likelihood of greater TV ($P=0.0581$) and predicted reduced likelihood of greater TSH ($P=0.00076$) whereas it was not associated with TN or TH. In multivariate analysis controlling for the effects of health related factors, history of goiter in the mother was found to be an independent predictor of TV (OR = 1.492 (1.083-2.055), $P=0.0144$) and TSH (OR = 0.616 (0.453-0.837), $P=0.0019$) but not of TN and TH. When multivariate models also included the other response variables, history of goiter in the mother remained independently associated with TSH but not with TV, whereas it also predicted the presence of TH (OR = 1.548 (1.076-2.227), $P=0.0185$). History of maternal goiter may have long-term impact on thyroid health of the female offspring. These alterations may be observed even after considerable time lapse at midife. The association between history of maternal goiter and their daughter's TSH may be more robust than the association between history of maternal goiter and daugter's TV.

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P487

Is there a paradigm shift for the evaluation and treatment of isthmic thyroid nodules?

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Introduction
Although the thyroid isthmus seems like a structure that connects bilateral lobes, it is an undiscovered area that needs to be explored. Currently, the data is evolving that the increase in the risk of malignancy is higher in the isthmic nodules, and extrathyroidal extensions and lymph node metastases are more common in isthmic-derived malignant thyroid nodules. Therefore, we aimed to compare the malignancy rate of isthmic and lobar nodules, the ultrasonographic features of isthmic and lobar nodules, and presence of lymph node metastases, distant metastases, and extrathyroidal invasions in malignant isthmic nodules.
Methods
In this retrospective study, we enrolled patients between the ages of 18-80 years, who had thyroid nodule/nodules cytology and/or pathology results from January 2009 to November 2020. 9504 nodules were selected for the analysis of US findings, cytopathology results, and malignancy rates.
Results
A median age of 56 (18-80) years with a Female to male ratio of [7618 (80.2%)/1886(19.8%)] were included in the study. 962 of the nodules were at isthmic localization; whereas 8542 nodules were at lobar localization. 803 nodules were surgically removed and resulted as malignant from histopathological evaluation. The median age of the patients with malignant nodules was 54 (18-80). Of the 803 malignant nodules, 704 nodules were (87.7%) PTC, 46 nodules (5.7%) were FTC, 35 nodules were (4.4%) MTC, 14 nodules 1.7% were Hurtle cell carcinoma, and 4 nodules (0.5%) were anaplastic thyroid carcinoma. 108 of the malignant nodules (13.4%) were located in the isthmus, whereas the majority of the malignant nodules (n:695, 86.6%) were located at the lobar parts (right or left) of the thyroid. When the metastasis patterns of isthmic and lobar thyroid cancers were examined, no significant relationship was found between isthmic and lobar cancers in terms of capsule invasion ($P=0.437$), muscle invasion ($P=0.294$), and lymph node metastasis ($P=0.476$). A significant correlation was found between nodule localization (isthmus-upper-middle and lower lobes) and malignancy ($P<0.0001$). In our logistic regression analysis, isthmic nodule localization was evaluated as an independent risk factor for malignancy (than lobar nodules)(OR: 1.35 95% CI, $P=0.008$). Nodules in the isthmus region were found to have a higher risk of malignancy compared to the lower lobes (OR: 1.88 95% CI, $P=0.005$).
Conclusions
We recommend, nodule localization has to be considered an additional risk factor when performing a Fine Needle Aspiration Biopsy (FNAB).

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Evaluation of Factors Determining Iodine Refractoriness in Thyroid Carcinoma

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Introduction
Radioiodine-resistant thyroid carcinoma is an important milestone in the treatment and follow-up of thyroid cancers. The biological defects of iodine uptake in thyroid cancer cells should be well known. In this study, we aimed to evaluate the clinical and pathological features and SLC5A5 gene expression status of iodine-refractory papillary thyroid carcinoma patients.
Material-Method
We studied SLC5A5 expression in 83 papillary thyroid carcinoma patients before radioactive iodine treatment was given. While 32 of these patients were radioactive iodine-refractory, 51 of them were cured with radioactive iodine on the follow-up. Biochemical, histopathological, and radiological data were gathered retrospectively.
Results
While the median $\pm$ SD age in the iodine-refractory thyroid carcinoma group was 56.56 $\pm$ 15.22, it was 46.82 $\pm$ 12.43 in the control group. The median value of the refractory patient's thyroglobulin was 278 (65-724), while it was 3.21 in the non refractory group (0.66–23.7). The mean age of 13 patients with refractory thyroid carcinoma who received chemotherapy was 65.77 $\pm$ 12.58. The mean age of 19 patients who did not receive chemotherapy was 50.26 $\pm$ 13.80. SLC5A5 gene expression increased in the iodine non-refractory PTK group and decreased in the iodine refractory PTK group. All these parameters and statistically significant ($P < 0.05$).
Conclusion
Advanced age (age $>$ 55 years) and a high postoperative thyroglobulin level (278 ng/ml) are effective in the development of iodine resistance in patients with differentiated thyroid carcinoma. In addition, the presence of advanced age in patients with iodine-refractory thyroid carcinoma is associated with the need for chemotherapy. Contrast expression changes in SLC5A5 gene expression may be a guide to better understand the pathophysiological mechanism of RAI refractory disease.

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Microscopic Calcifications Isolated from Thyroid Nodule Fine Needle Aspiration Can Serve as Biomarkers of Thyroid Nodule Malignancy

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Background
When US characteristics and the diameter of a thyroid nodule (TN) justify further evaluation to rule out or to establish the diagnosis of thyroid cancer (TC), fine needle aspiration (FNA) biopsy for cytology (FNAC) is indicated. A major limitation of FNAC is the high rate of indeterminate significance (~30%) results, which require further evaluation. Although recently introduced molecular testing contributed to the ability to differentiate benign from malignant TNs, these approaches are costly, and not available worldwide. Punctate calcifications detected within a TN by neck US are considered a high-risk feature for TC. We hypothesized that the small amount of material that remains in the syringe at the end of the FNA procedure contains microscopic calcifications (MCs), that may differentiate benign from malignant TNs, by chemical analysis for composition and morphology.
Aim
To assess the diagnostic potential of MCs within TNs obtained during routine FNAC procedure.
Methods
In this single-center proof-of-concept study, samples were collected between 11/2020 and 12/2022 during FNAC procedures, conducted as clinically indicated. Clinical decisions were made according to the accepted guidelines based on thyroid US and cytological findings. Comparisons between the final diagnosis of a TN as benign or malignant and the results of the thorough compositional and morphological MCs analyses were conducted retrospectively.
Results
Samples from 124 patients were collected and sent for chemical analysis in parallel with the routine cytological evaluation. Samples from 26 patients were used for protocol development, and 35 patients were still under clinical evaluation. The remaining 63 patients underwent full clinical evaluation, and FNA samples from these patients were subject to the MCs isolation protocol. In 52/63 patients (82.5%), FNA MCs were identified. Interestingly, all 11 patients without identifiable MCs were diagnosed with benign TNs. The final study cohort included 30 patients with benign TNs (median age: 54 years [range: 26-76 years], 83.3% females), and 22 patients with TC (median age: 42 years [range: 18-80 years], 63.6% females). Morphologically, while MCs from patients with TC were spherical, MCs from benign TNs were crystals with sharp edges. Regarding elemental composition, zinc was present in 91% and 7% of MCs obtained from patients with final diagnosis of TC and benign TN, respectively.
Conclusion
The presence of zinc in MCs isolated from samples collected during routine FNAC can offer value as a biomarker for TC.

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Challenges in the management of endocrine complications after hematopoietic stem cell transplantation – could it be reconstitution Graves' disease?

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Background
The rapid advancements in the field of allogenic hematopoietic stem cell transplantation (allo-HSCT) and better management of acute postprocedural complications have led to increased life expectancy, but at the same time to higher incidences of long-term complications. Conditioning regimens (chemotherapy, total body irradiation), immunosuppresive treatments and immune dysregulation threaten endocrine and metabolic functions, leading to late effects, including hypogonadism and infertility, thyroid dysfunction or steroid-induced diabetes and dyslipidemia, associated with increased cardio-vascular risk. Even though, thyroid function abnormalities are one of the most prevalent conditions encountered after HSCT, Graves' disease is rarely seen, but can appear as a result of immune reconstitution syndrome, either by transfer of pathogenic auto-reactive lymphocyte clone from donor to recipient or by loss of immunotolerance secondary to graft-vs-host disease (GVHD).
Case report
A 20-year old female received an allo-HSCT from a related donor(brother) for acute myeloid leukemia without maturation (M1) in November 2019. The conditioning regimen included cytarabine, idarubicine, etopozide and methyl-prednisolone. In August 2021, the patient developed an active form of cutaneous chronic graft-vs-host disease with morphea-like lesions, for which high doses of methylprednisolone were started. In December 2021, she presented to our departement for premature ovarian failure secondary to chemotherapy and evaluation for other endocrine and metabolic complications. Continuous combined hormone replacement therapy was introduced for menopausal symptoms. Subsequently, the patient developed hematocolpos secondary to vulvovaginal cGVHD for which she underwent dilatation. At the next follow-up in our department, her thyroid function tests revealed a TSH level of 0.059 µIU/ml (0.3-3.6 µIU/ml), fT4 1.08ng/dl (0.8-1.7ng/dl) and fT3 60.7 ng/dl (76.3-220.8 ng/dl). Her thyroid ultrasound was normal. Even though, her thyroid function abnormalities are consistent with the effects of high dose corticosteroids, subclinical hyperthyroidism caused by Graves' disease in connection with a post-transplant immune reconstitution syndrome cannot be excluded, as thyrotropin receptor antibodies were found increased (TRAb = 5.06 UI/l, normal 0-1.75 UI/l). Nevertheless, we were not able to perform TSI for differential diagnosis. Moreover, diabetes mellitus (fasting glucose = 132 mg/dl) and dyslipidemia (total cholesterol = 476 mg/dl, triglycerides = 716 mg/dl) were diagnosed.
Conclusions
As survivorship after HSCT increases and endocrine complications become more frequent, emphasis should be placed on the importance of a long-term multidisciplinary follow-up, in order to recognise and treat endocrinopathies before clinical impact, thus optimizing quality of life. Furthermore, HSCT offers an unique insight into the pathogenesis of autoimmune disease, such as Graves' disease.

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P491

A life threatening manifestation of severe hypothyroidism

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A 29 year old lady with a past history of seronegative rheumatoid arthritis, Vitamin B12 deficiency, autoimmune hypothyroidism and fibromyalgia who had feeling unwell with a left sided headache for a few days had a fall at home witnessed by her friend. She was noted to be in peri arrest state by ambulance crew on their arrival. Agonal breathing was noted and monitor revealed VF. She was given 5 DC shocks with return of spontaneous circulation and regained consciousness. She was transferred to ITU where her initial obervations showed oxygen saturation of 94% on oxygen with a respiratory rate of 26 and pulse rate of 106 per minute and a GCS of 15 with a glucose of 12.1 mmol/l. Her recent thyroid biochemistry had revealed poorly controlled hypothyroidism with a TSH of 160.41 miu/l. She had a long history of poor compliance with her thyroid medication and the plan prior to her hospital admission was her to have had a supervised levothyroxine adminstration and absorption test to probe for any issues with malabsorption which unfortunately she could not attend. She was intially commenced on iv liothyronine and hydrocortisone along with fluid resucitation and broad spectrum antibiotics as a CTPA showed widepread lung consolidation with however no pulmonary embolism. A bedside echocardiogram showed evidence of moderate to severe LV impairment with an ejection fraction of 35-40% and a small posterior pericardial effusion of maximum size of 1.3 cm. She was commenced on Ramipril. She made good progress and was switched to oral liothyronine and levothyroxine on day 2 of her stay on ITU. Her TSH showed good recovery with a value of 38.9 on day 3 with further improvement to 20.22 on day 5. An ECHO 2 weeks later showed a slight improvement in her LV function with an EF at 45%. The patient was transferred to the medical ward and made steady progress. Serial ECHO showed a reduction in the pericardial effusion with further improvement in LV function. The patient was subsequently well enough and stable to be discharged home. This case highlights the reversibility of cardiac dysfunction induced by severe hypothyroidism with focussed thyroid replacement in a patient with a history of poor compliance with the management of her hypothyroidism. Severe hypothyroidism can cause reduced ventricular filling and decreased cardiac contractility which in turn leads to reduced cardiac output which in the extreme case of severe hypothyroidism can be life threatening.

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P492

Resistance to Thyroid Hormone Beta in a 12-Year-Old Patient: Clinical, Laboratory, and Molecular Characteristics

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Background
Resistance to thyroid hormone beta (RTHβ) is an inherited syndrome of reduced tissue responsiveness to thyroid hormones (THs). It is driven in 85% of cases by mutations in the thyroid hormone receptor beta (*THRb*). The estimated incidence is 1:40.000 to 1:19.000 live births. We report the clinical, laboratory, and genetic analysis of a patient with this disorder.
Case report
A 12-year-old boy with a history of Attention-Deficit/Hyperactivity Disorder was referred to endocrinological evaluation due to hyperactive, impulsive behavior, insomnia, palpitations, heat intolerance, and perspiration. Physical examination was unremarkable except for resting tachycardia and hypertension. Thyroid function tests (TFTs) showed normal thyroid-stimulating hormone (TSH) of 2.38 uIU/ml (normal range: 0.4-4.0), elevated free thyroxine (fT4) of 2.48 ng/dl (0.7-1.3), free triiodothyronine (fT3) of 10.9 pg/ml (2.4-4.1) and reverse T3 (435 pg/ml; 90-215) levels. He was not taking any medications that could have affected thyroid labs. Repeat TFTs using a different assay showed a similar pattern. Antithyroid peroxidase and TSH receptor antibodies were not detected. Sex Hormone-Binding Globulin (SHBG), a peripheral marker of THs action, was in the euthyroid range. A diffuse cystic goiter was revealed on ultrasound. The magnetic resonance imaging identified a 5 mm hypointense area in a slightly hyperplasic pituitary. His father showed hormonal abnormalities consistent with RTHβ. T3 and Thyrotropin-releasing hormone (TRH) was not available for dynamic tests. A heterozygous missense mutation in the *THRβ* gene (c.1012C>T) was identified. Tiratricol was prescribed thereafter.
Discussions
Elevated serum THs accompanied by unsuppressed TSH are suggestive of RTHβ. However, alternative diagnoses (assay interferences, thyroxine-binding globulin abnormalities, and familial dysalbuminemic hyperthyroxinemia) should be excluded first by measuring free THs with equilibrium dialysis and T4-binding panel. First-degree relatives hormonal testing, a-subunit/TSH ratio, markers of THs action (SHBG, Type I Collagen C-Terminal Telopeptide), pituitary imaging, dynamic tests with T3 and TRH are used to discriminate between RTHβ and thyrotropinoma. As in our patient, a pituitary lesion mimicking thyrotropinoma may appear in RTHβ as an incidental finding; although it can result from thyrotropes enlargement after a longstanding absence of negative feedback. Genetic testing is regarded as the gold standard for definitive diagnosis. *THRβ* c.1012C>T affects a highly conserved amino acid (p.Arg338Trp) in the *THRβ* T3-binding domain and was classified as pathogenic.
Conclusions
In the setting of normal TSH and elevated THs, after ruling-out artifactual laboratory interference, there is a high suspicion for RTHβ. Alternative diagnoses should be excluded as they have completely different management approaches.

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P493

Role of thyroid hormones in the development of neurodegeneration in rats

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Introduction
Neurodegeneration is one of the most common condition accompanied Diabetes Mellitus, Parkinson's and Alzheimer's diseases. Although its mechanisms intensively studied for many years, some questions of pathogenesis remain unclear. The aim of the study was investigate the effects of thyroid hormones and some neurotransmitters on the cerebral cortex of rats with experimental neurodegeneration.
Materials and methods
Series of experiments were carried out on 45 purebred white rats were divided into 3 groups: control, animals given a neurotoxins such as thiamazole (second group) and AlCl3 (third group) for neurodegeneration models. In the end of experiments rats were sacrified, blood samples taken by cardiac puncture, hippocampus, cortex and other parts of the brain taken separately and homogenised. In blood serum T3, T4, TTG and tau protein concentrations were determined, also in samples from hippocampus, cortex and other part of the brain based on enzyme immunoassay kits. Determination of the content of neurotransmitters aspartate, glutamate, gamma-aminobutyric acid (GABA) level in samples were measured using thin-layer chromatography. The amount of dopamine and noradrenaline in the homogenate of the hippocampus and cortex of the brain determined by column chromatography, and acetylcholine was determined spectrophotometrically.
Results
Rat models with neurodegeneration were obtained 14th day after taken of neurotoxins. Blood serum T3, T4 levels were not significantly differs between the groups and were in normal ranges. Interestingly, in rats with both neurodegeneration models significant decreasing in the level of T3 in the homogenate of the hippocampus and cortex, but not in other parts of the brain were found. Moreover, neurotransmitters level were disturbed i.e. increasing of glutamate and aspartate, GABA level, also decreasing of amount of noradrenaline and dopamine in the homogenates of the hippocampus and cortex of the brain were determined in rats with neurodegeneration. Decreasing level of thyroid hormones locally in hippocampus and cortex of the brain and abnormal neurotransmitters level probably was one of the main causes of the disturbance of cognitive functions in the rats.
Conclusion
Experimental neurodegeneration in rats revealed decreasing of thyroid hormones level locally in the homogenates of the hippocampus and cortex of the brain, which accompanied with disturbed level of glutamate and aspartate, GABA levels, also decreasing of amount of noradrenaline and dopamine, which affected rats cognitive function.

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The utility of salivary thyroid hormones in assessment of thyroid function

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Introduction
Saliva is an interesting alternative to blood in clinical evaluation of endocrine function. Certain advantages of saliva collection must be considered, when comparing with conventional blood sampling. Vital arguments are that procedure is easy, non-invasive and stress-free. The studies on correlation between salivary and serum thyroid hormones are scarce and contradictory. The goal of our research was to assess if salivary thyroid hormone levels reflect serum concentration.
Methods
This is a prospective study with a consecutive enrollment of patients routinely referred for thyroid hormone's evaluation. We recruited 109 patients with various thyroid disorders. We assessed TSH, ft3 and ft4 concentration in serum with electrochemiluminescence (ECLIA) immunoassays and chemiluminescence immunoassay (CLIA). Serum levels of anti-thyroid antibodies were measure with ECLIA. In saliva, ft3 and ft4 levels were evaluated by the liquid chromatography with tandem mass spectrometry (LC-MS/MS) analytical technique. Venous blood samples were collected in the morning, after an overnight fast. Saliva samples were obtained in the morning into special Salivette® tubes. Saliva was picked up after at least 30 minutes of eating, drinking, smoking, or chewing gum.
Results
There was a consistency between ECLIA and CLIA methods for serum assessment of TSH, ft3 and ft4. In the whole group ($P<0.001$, R 0.575) and in the subgroup with TSH within reference interval ($P<0.001$, R 0.570) salivary ft3 and ft4 were positively correlated. Then we evaluated correlation between serum and salivary hormone concentrations, according to TSH reference ranges. Serum ft4 correlated positively with salivary ft4 in entire group (ECLIA $P<0.001$, R 0.355; CLIA $P<0.001$, R 0.384), in subgroup with TSH within reference interval (ECLIA $P=0.027$, R 0.256; CLIA $P<0.001$, R 0.263) and in one with TSH above normal limit (CLIA $P=0.014$, R 0.712). Adversely, serum ft3 correlated with salivary hormone only in patient with TSH below normal value (CLIA $P=0.017$, R -0.802; ECLIA $P=0.011$, R -0.826). Then we assess how levothyroxine therapy for hypothyroidism influence serum/saliva thyroid hormones correlations. Salivary and serum hormones were correlated only in naïve treatment patients. We evaluated also if anti-thyroid antibodies have an impact on salivary and serum thyroid hormones.
Conclusions
Our study indicated that salivary thyroid hormones to a certain degree mirror levels of their serum equivalents. Even, in patients with anti-thyroid antibodies, but not on levothyroxine treatment, saliva assessment may be of clinical value. Our research provide a basis for future studies concerning usefulness of saliva in evaluation of thyroid function.

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Weight Variability with the Treatment of Graves' Disease in Adults

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Introduction
Graves disease (GD) is a frequent cause of primary hyperthyroidism and often presents with weight loss. Weight gain beyond the premorbid state is often reported and could be a challenge during patient's management. Treatment modalities, disease remission and biochemical parameters at the diagnosis have been described as predictors of weight changes in patients with GD.
Objectives
To evaluate the determinants of weight changes in GD treated patients.
Methods
Retrospective, observational and longitudinal study of patients with the diagnosis of GD and at least six months of follow-up, with available data regarding baseline, premorbid and post-treatment weight. Laboratory and demographic variables, including body mass index (BMI), were also recorded.
Results
The sample included 122 patients (95 females) with a median age at the diagnosis of 48 years-old (IQR 21). Almost 34% of the patients documented some weight loss during the state of hyperthyroidism. Hyperthyroidism was responsible for a mean loss of 5,7 $\pm$ 7,8 kg, with a mean BMI reduction of 0,75 (IQR 3,00) kg/m^2. Moreover, patients with weight loss before treatment presented a lower premorbid BMI (22,4 $\pm$ 2,7 vs 25,1 $\pm$ 4,8 kg/m^2, *P*-value 0,027). On the other hand, after starting treatment, a weight gain was observed in 59,2% of patients, and excessive weight gain (final weight above premorbid weight) in 23,8% of them. Patients with weight gain after treatment were mainly women (78%), with a mean age of 47 $\pm$14,7 years. These patients were also more frequently smokers (*P*-value 0,034) and presented higher prevalence of hypothyroidism after treatment (*P*-value 0,008). All patients considered underweight (BMI <18 kg/m^2) presented a weight gain during treatment (*P*-value <0.001). Curiously, excessive weight gain was more common between individuals that did not lose weight before treatment (*P*-value <0.001). Hypothyroidism after treatment of GD was more prevalent among those with excessive weight gain (*P*-value <0.001). Finally, there was no difference in baseline TSH, TSH-receptor antibody levels, free T4 or free T3 serum levels between patients regardless of their weight changes.
Conclusions
Our analysis shows that GD patients with a lower premorbid BMI presented with a higher weight loss at the diagnosis. Also, excessive weight gain was more common between individuals that did not lose weight before treatment. These results support the evidence that other factors, especially premorbid patient's BMI, may determine weight changes in GD patients, regardless of their analytical serum endocrinological profile and disease management.

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Amyloid Goiter, Papillary Thyroid Microcarcinoma and Diffuse Thyroid Lipomatosis – a case report of a rare association

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Introduction
Amyloidosis is a disease characterized by the accumulation of an amorphous proteinaceous material, known as amyloid, in various organs and tissues of the body. Amyloid goiter is a remarkably rare pathologic condition due to thyroid massive amyloid infiltration of amyloid light chain (primary) or amyloid A (secondary amyloidosis) proteins.
Case
54 year-old male, with known history of chronic tophaceous gout medicated with anakinra and prednisolone, obesity (BMI 36.0 Kg/m2), obstructive sleep apnea, heart failure with preserved ejection fraction and an enlarged multinodular goiter. Relevant thyroid nodules were found in the right lobe (4.5 cm, TIRADS 4) and in the left lobe (3.7 cm, TIRADS 2 and 2.6 cm, TIRADS 2). Fine needle aspiration cytology to the TIRADS-4 lesion was non-diagnostic (*Bethesda I*). Sometime later compliants of cervical compressive symptoms such as dysphagia were found. The ultrasound revealed an overall enlargement of the thyroid gland and its nodules with significant tracheal deviation. Thyroid function tests revealed a TSH 0.96 µUI/ml (RR: 0.30 - 3.18) and a T4L 1.57 ng/dl (RR: 1.01 - 1.65) with negative anti-thyroid peroxidase (TPO) and anti-thyroglobulin (TG) antibodies. A total thyroidectomy was performed. The thyroid weighed 125g and consisted of amyloid lesions associated with diffuse lipomatosis and multiple focal and bilateral papillary microcarcinomas (dominant with 2mm). Proper search for systemic amyloidosis was performed without any discovery. At the last follow-up, he had an excellent biochemical response with undetected Tg level and no evidence of amyloid recurrence.
Conclusions
Deposition of amyloid in the thyroid gland is a rare condition. In patients with a rapid enlargement of the goiter and a history of chronic inflammatory diseases, clinicians should suspect of amyloid involvement. This excessive growth can cause compression of the surrounding structures and warrant a total thyroidectomy. Papillary thyroid carcinoma has been rarely associated to amyloid goiter.

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Course of Papillary Thyroid Carcinoma Diagnosed in Childhood and Adolescence and Followed Through Adulthood: Experience from a Tertiary Referral Center

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Introduction
Differentiated thyroid cancer accounts for 1.5% of all pediatric malignancies. Papillary thyroid cancer (PTC) is the most common subtype and is associated with more advanced disease at diagnosis compared to adults. The aim of this study was to identify long-term outcomes of pediatric PTC.
Methods
Records of 30 patients with PTC diagnosed in childhood and adolescence and followed up at Istanbul Faculty of Medicine were reviewed retrospectively.
Results
The mean age of 30 patients (21 females, 9 males) at diagnosis was 14,7±2,4 years (range, 7 to 18). Mean duration of follow-up was 126,8±45,2 months. Five patients had history of radiation therapy (RT); mean duration from RT to diagnosis of PTC was 7,2±2,4 years. Mean nodule diameter was 1,54±1,32 cm, and fine-needle aspiration biopsy was Bethesda II in 6,6%, III in 6,6%, IV in 10%, V in 26,6%, and VI in 46,6%. The patients underwent total thyroidectomy ($n=9$), or total thyroidectomy with central lymph node dissection ($n=9$) or total thyroidectomy with central and lateral lymph node dissection ($n=12$). The tumor was located in both lobes in 43,3% of the patients, in left lobe in 30%, in right lobe in 20%, and in isthmus in 3.3%. The mean tumor diameter was 1,56±1,47 cm (range, 0,1 to 6), and was microcarcinoma in 12 of the patients. Histopathological subtype was available in 28 patients (follicular variant $n=13$, classic $n=9$, encapsulated follicular $n=3$, tall cell $n=1$, macrofollicular $n=1$, hobnail $n=1$, diffuse sclerosing $n=1$). Chronic lymphocytic thyroiditis was detected in 10 patients. Six patients had BRAF mutation. There were 5 patients with T2 and 2 patients with T3 disease. At diagnosis, half of the patients had lymph node metastasis to the neck or upper mediastinum (N1a=5, N1b=10), and 2 also had lung metastasis. Of 10 patients with N1b, 7 had multicentric disease and vascular invasion, and 6 had lymphatic invasion. Eight low-risk patients still in remission were treated with only TSH-suppressive levothyroxine. Post-operative radioactive iodine (RAI) treatment was administered to 22 patients [median number of administration was one (range 1-7), median cumulative dose was 150 mCi (range 50 to 1100)]. Sixteen patients had excellent response following single ($n=13$) or multiple (2 for persistent and 1 for recurring disease after 100 months) RAI administrations. Remaining 3 patients had structural incomplete and 3 had indeterminate response.
Conclusions
Although PTC presented at more advanced stage in childhood and adolescence, the response to treatment was fairly good with appropriate management.

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Performances of ABEI-based automated immunoassays thyroid function tests

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Background
Diagnosis and monitoring of thyroid diseases rely on thyroid function tests. Testing for Thyroid Stimulating Hormone (TSH) and free thyroxin (FT4) are frontline assays for the diagnosis of hyper- and hypothyroidism. Measurement of TSH receptor autoantibodies (TRAB) is pivotal for the diagnosis of Graves' disease. Our study objective was to determine the performances of ABEI-based automated immunoassays for measurement of TSH, FT4 and TRAb.
Methods
Performances of the Maglumi® 800 TSH, FT4 and TRAb chemiluminescent immunoassays that applies ABEI labels were determined. Imprecision of assays was assessed with control materials. Method comparison was performed with Cobas electrochemiluminescent assays for TSH and FT4 and with Kryptor Compact Plus assay for TRAb. Reference intervals were also confirmed with samples from healthy volunteers.
Results
Between-run imprecision coefficients of variation were 7.1% for concentrations of 3.3 IU/ml for TSH, 4.4% for concentrations of 15.0 pg/ml for FT4 and 2.2 % for concentrations of 3.6 IU/l for TRAb, respectively. Passing-Bablok regression analysis showed a slope of 1.07 and an intercept of -0.06 for TSH, a slope of 1.03 and an intercept of 0.99 for FT4. For TRAb assay, the Kappa coefficient of concordance with the TRAK method was 0.79. Reference intervals were 0.4 – 2.6 IU/ml for TSH and 8.0 to 17 pg/ml for FT4. The 99th percentile of the reference of the TRAb assay was 1.38 IU/ml.
Conclusions
The ABEI-based automated immunoassays showed good analytical performances for the Maglumi® TSH, FT4 and TRAb and our study confirmed reference intervals for those assays.

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Radioiodine therapy outcomes in benign thyroid disease at the University Hospital of Wales, UK

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Background
Radioiodine therapy (I-131) is commonly prescribed for benign thyroid disease in keeping with recommended guidelines.
Aims
To determine the effectiveness of I-131 in treating benign thyroid disease and the rates of hypothyroidism following treatment and by diagnosis.
Methods
We identified 100 patients who received radioiodine therapy between November 2013 and June 2015 from a database held in the Medical Physics Department at the University Hospital of Wales, Cardiff, UK. Patient group: 18 male, 82 female; mean age: 58 (15-91)y. Mean activity of I-131 administered: 556 (529-572) MBq. Diagnosis: Graves' disease (52%), solitary toxic nodule (15%), toxic multi-nodular goitre (MNG) (21%), subclinical hyperthyroidism (12%). 89% were cured with a single treatment of I-131, 10% required a second therapy and 1% a third. Hypothyroidism: 67% patients became hypothyroid, requiring levothyroxine replacement. Rates of hypothyroidism according to diagnosis: Graves' (49/52 = 94%), solitary toxic nodule (6/15 = 40%), toxic MNG (7/21 = 33%), subclinical hyperthyroidism (5/12 = 42%), X 2 (6, $n=100$) = 40.06, $P<.001$. There was no correlation between development of hypothyroidism and smoking status or age. Median time to hypothyroidism was 4 (1-94) months, mode 2 months. There was no correlation between time to hypothyroidism and smoking status or age.
Conclusions
Most patients who received I-131 were female, and had a a diagnosis of Graves' disease. 89% were cured with following a single treatment of I-131, and overall 67% became hypothyroid, most 2 months following therapy. There was a statistically significant different in the rates of those who became hypothyroid according to diagnosis, with the highest rates of hypothyroidism in those receiving I-131 for Graves' disease.

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The iodine study in pregnancy: no correlation between serum thyroglobulin and urinary iodine concentration

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Background
Despite obligatory iodination of salt in the Czech Republic, pregnant women with higher demands on iodine intake may be at risk of iodine deficiency with potentially negative consequences for the course of pregnancy and foetal development. Determination of urinary iodine concentration (UIC) is a conventional but not widely available method used to estimate the iodine status. Based on previous studies, serum thyroglobulin (Tg) could serve as a more convenient marker of iodine deficiency in preschool children and adults. This study aimed to investigate the potential use of Tg as a marker of iodine status in pregnancy.

Patients and methods
UIC from the morning urine sample, biochemical thyroid tests — serum concentration of thyroid stimulating hormone (TSH), free thyroxine (FT4), antibodies to thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) and serum thyroglobulin (Tg) were measured, and thyroid ultrasound (US) was performed in 187 pregnant women in the first trimester of pregnancy.
Results
Overall, inadequate iodine supply in the investigated group of pregnant women was found (median UIC 119.2 μg/l). In the group of women taking oral iodine supplements with ≥ 100 μg of elemental iodine daily, the IUC was significantly higher compared to the group of women taking supplements with 100 μg of iodine or no supplements (median IUC 137.85 μg/l vs. 103.50 μg/l, $P = 0.002$). We found no significant correlation between serum Tg and UIC. Serum Tg was significantly higher in euthyroid TPOAb positive women with US pattern of autoimmune thyroiditis as compared to euthyroid TPOAb positive women with normal US and controls (median Tg 25.65, 7.9 and 8.5 μg/l, respectively, $P = 0.0009$).
Conclusions
Serum Tg was no reliable marker of iodine deficiency in pregnant women in our study. In TPOAb-positive women, serum Tg could distinguish between actual autoimmune inflammation of the thyroid gland and simple serum TPOAb positivity, but further studies are needed. The study was supported by the Charles University, project GA UK No. 265221

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An unremarkable presentation but signs of Grave danger: Never forget the thyroid function

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Introduction
Profound thyrotoxicosis commonly presents with heat intolerance, sweating, weight loss, palpitations, tremor, goitre and eye signs in the case of Grave's disease. Typically, thyroid storm is differentiated by marked volume depletion, congestive cardiac failure, cardiac arrhythmias, confusion, nausea and vomiting, often with extreme agitation. The wide-ranging and systemic manifestations associated with profound hyperthyroidism are mediated through the thyroid hormone receptor present in most tissues throughout the body.
Case Presentation
A 16 year old female presented to the emergency department with increasing shortness of breath over the last two months. She had a previous history of surgically-corrected patent ductus arteriosus, bilateral sensorineural hearing loss and depression and anxiety, with no previous history of endocrine disease. She was apyrexial, found to be tachycardic and tachypnoeic with an elevated jugular venous pressure, but no signs of thyrotoxicosis. Her biochemistry was notable for free T3 > 50 pmol/l, free T4 > 100 pmol/l, TSH < 0.01 mU/l, thyroid-stimulating immunoglobulins 27.30 IU/l and a peak NT-proBNP of 29,258 ng/l. She was admitted for further investigation and treatment. Echocardiogram demonstrated biventricular failure with a left ventricular ejection fraction of 35% and severe tricuspid regurgitation associated with right ventricular failure. She was initially treated with carbimazole, propranolol and hydrocortisone. She deteriorated rapidly with increasing breathlessness and became unresponsive requiring prolonged intubation and intensive care unit stay. She was transferred to the specialist tertiary centre to consider mechanical bridging therapy and heart transplant but she recovered with milrinone infusion and was repatriated for continuation of management. She was extubated successfully after 3 weeks and subesquently completed ward-based rehabilitation. On discharge, her hyperthyroidism and decompensated heart failure status resolved, and her most recent echocardiogram observed a left ventricular ejection fraction of 45-49% with trivial-mild tricuspid regurgitation and a NT-proBNP of 179 ng/l. Her free T3 was 6.2 pmol/l, free T4 16.4 pmol/l and TSH < 0.01 mU/l. She was discharged on carbimazole 15 mg once daily.
Conclusion
The key learning points from this case are that severe thyrotoxicosis can present with shortness of breath and no other typical hyperthyroidism symptoms, and patients can present with severe heart failure in the absence of Grave's disease signs and symptoms. Importantly, the treatment of Grave's thyrotoxicosis can resolve cardiac impairment, therefore we recommend assessing thyroid status, an inexpensive test, early in such cases to prevent Grave complications.

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Long-Term Effects of Radioiodine Treatment on Thyroid Functions, Thyroid Volume, Nodule Volume and Ultrasonographic Features in Patients with Toxic Adenoma and Toxic Multinodular Goitre

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Background
Radioiodine(RAI) has been used to treat hyperthyroidism for more than seven decades. Effects of RAI treatment on thyroid function tests(TFT), risk of hypothyroidism, gland and autonomous nodule volumes and on ultrasonographic features in toxic adenoma (TA) and toxic multinodular goitre TMNG patients, have been previously studied by ourselves and other. However, studies evaluating ultrasonographic changes in thyroid and toxic nodule volumes usually have a follow-up period less than 36 months. Thus we aimed to study the long-term effects of RAI treatment on thyroid functions, ultrasonographic morphology and volume changes in patients with TA and TMNG.
Methods
Thyroid function tests and ultrasonography (US) reports of patients diagnosed with TA or TMNG between the years 2000 and 2021 were retrospectively analysed.
Results
We included 100 patients ($n = 65$ TA, $n = 35$ TMNG) whom thyroid function and US reports were obtained before and at least 36 months post-RAI. At the end of the median follow-up of 7.3 ± 0.3 years (TA, 6.6 ± 0.5 years; TMNG, 8.5 ± 0.7 years), the mean thyroid volume (TV) reduction in patients with TA and TMNG was mean ± sd, 56.6 ± 3.1% and 51.1 ± 6.7%, respectively. Mean volume decrease of all toxic nodules was 80.5 ± 1.9%. When the TA patients were divided into age groups as < 50 and ≥ 50 years, the TV reduction was significantly higher in younger patients(64.5 ± 4.7% vs 53.1 ± 3.8%, $P < 0.05$). One year after RAI treatment, the maximal volume reduction of the toxic nodules (TN) was 66.5%. The volume of the thyroid and TN was significantly reduced up to 12 years ($P < 0.01$) after RAI treatment. Between 3 and 10 years after RAI therapy, the annual incidence of hypothyroidism was 2.0% and 1.5% in the TA and TMNG groups, respectively. Patients who developed hypothyroidism in both TA and TMNG groups had significantly smaller pre-treatment TV when compared to euthyroid patients [i.e. 51.1 ± 4.7 mL and 21.4 ± 1.8 mL ($P < 0.05$)]. Compared with pretreatment sonography findings, TN were more frequently solid, hypoechoic and macrocalcified in post-RAI ultrasounds ($P < 0.01$).
Conclusions
The volume of thyroid gland and toxic nodules continuously decreases, as the risk of hypothyroidism increases up to 10 years after RAI treatment. Thus, follow up to check thyroid functions should continue. In post-RAI examinations, toxic nodules may show ultrasonographic features suspicious for malignancy. Hence history should include previous RAI treatment and old scintigraphy scans should be evaluated to avoid unnecessary procedures and non-diagnostic biopsy results.

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P503

Thyroid status in patients after COVID19 in iodine deficiency region

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Introduction
Coronavirus infection COVID19 spread by Sars-Cov-2 virus were announced by WHO as a pandemics in the end of 2019. As shown in many studies virus affects whole body, particularly endocrine system. There were information about thyroid disturbances after COVID19 infection. Fergana valley of Uzbekistan is an endemic region with high degree of iodine deficiency. The aim of our study were investigate impact of COVID19 on thyroid function in people living in iodine deficiency region.
Material and methods
Study conducted in 84 people who had no any problems with thyroid gland previously and were admitted and treated from COVID19 in hospital of Fergana region. Patients' clinical and anamnestic data, also data from charts were collected and analyzed. Thyroid gland were observed by palpation, thyroid hormones TSH, T3, free T4, and anti-TPO level were detected by RIA kits, structure of thyroid gland were estimated by ultrasound.

Results
80% of observed people who were suffered from COVID19 were women and 20% were men. Palpation of thyroid gland shown that all of them had enlargement of thyroid gland (5%) or/and nodules (95%). Thyroid gland examination by ultrasound revealed that 30 (35%) patients had I-II degree of thyroid enlargement, 35 (42%) patients had autoimmune thyroiditis, 19 (23%) patients had nodular goitre. When examine the thyroid hormones level were shown that 58% patients were in euthyroid state, 36% patients had subclinical hypothyroidism, and 6% patients had manifest hypothyroidism. It seems that iodine deficiency more predisposed thyroid gland to Sar-Cov-2 virus.
Conclusion
In people who lives in high iodine deficiency region after COVID19 thyroid status were affected in 42% and structure were affected in all patients, where 35% was thyroid gland enlargement and in 42% had autoimmune thyroiditis and 23% had nodular goiter.

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Incidence of congenital hypothyroidism in Lithuania: data from the National New-born screening program, 2002-2019

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Background
Congenital hypothyroidism (CH) is one of the most common preventable causes of mental retardation and intellectual disability. The overall incidence of CH ranges from 1 in 3,000 to 1 in 4,000 live births, with variation worldwide among different ethnicity [1]. During the period 1993–2000 the incidence of CH in Lithuanian population was estimated as 1 in 4800 live births [2]. The aim of present study was to determine the incidence of CH among new-borns in Lithuania.
Methods
The study was conducted as a part the nationwide NATRIJOD program aimed to evaluate sodium and iodine status in Lithuania. We retrospectively analyzed the results of neonatal thyroid-stimulating hormone (nTSH) tests from the National new-born Screening Program for congenital hypothyroidism database during the period 2002–2019; this reflected about 18% of the total population. According to the screening methodology, heel-prick blood samples of new-borns were collected on filter paper cards. Results of samples collected more than 48 h after the first feeding were analyzed. The nTSH concentration was measured in dry blood spots (DBS) using a fluorometric enzyme immunoassay (Labsystems). Anonymized results of nTSH tests from 517498 cards were retrieved in total. Inadequately sampled 640 DBS were excluded, data of 516858 live-borns were analysed. New-born screening for CH was based on measuring nTSH using a 10 mU/l cut-off and diagnosis of CH was confirmed after repeated evaluation of new-born.
Results
Total of 100 new-borns were diagnosed with CH during study period. Number of CH each year was different lowest in 2004 – 3 cases with CH and highest in 2008 – 17 cases of CH. The highest incidence of CH in Lithuania was observed in 3 counties – Vilnius (29 cases during 19 years), Kaunas (34 cases during 19 years) and Klaipeda (13 cases during 19 years), where 60% of the country's population live. During the period 2002–2019 the incidence of CH in Lithuanian population was estimated as 1 in 4784 live births.
Conclusions
The overall incidence of CH is low in Lithuania. The study revealed significant geographical variations of CH incidence in Lithuania, depending on population density.
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P505

Thyroid hormones resistance, lipid profile and insulin resistance in autoimmune thyroiditis

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Introduction
Anomalies of glucose metabolism and insulin resistance are common in patients with hypothyroidism. Some studies suggests that euthyroid autoimmune thyroiditis (AIT) may also be associated with changes of glucose metabolism and insulin resistance. The role of thyroid hormones resistance in this context is still uncertain.
Aim
To evaluate the relationship between thyroid hormones resistance, insulin resistance and lipid profile in euthyroid patients with AIT.
Methods
We evaluated a sample of 40 patients with AIT. We assessed thyroid function tests and calculated the resistance to thyroid hormones [Parametric Thyroid Feedback Quantile-Based Index (PTFQI)]. Thyroid antibodies, lipid profile, high-sensitivity C-reactive protein, B12 vitamin, folic acid, anti-thyroid antibodies, and the insulin resistance indexes [HOMA-IR, HOMA-B, QUICKI (Quantitative Insulin Sensitivity Check Index), HISI (Hepatic Insulin Sensitivity Index), WBISI (Whole-Body ISI) and IGI (Insulinogenic Index)] were also evaluated. We divided patients in two groups: TSH <2.00 μUI/ml and TSH >2.00 μUI/ml. All patients had normal levels of TSH, FT3 and FT4. The statistical analysis was done with the Student's t-test and Pearson correlation. We considered a two-tailed P-value of <0.05 significant.
Results
The mean age was 54.4 $\pm$ 13.6 years and 95 % were female. In the total group, we found a negative correlation between PTFQI and Lp(a) ($r=$-0.37; $P=0.04$). Patients with TSH >2.00 μUI/ml had significant higher levels of PTFQI ($0.912\pm$ 0.072 vs $0.701\pm$ 0.155; $P\leq$ 0.001). Patients with TSH >2.00 μUI/ml had significant higher levels of A1c (5.73 ± 0.35 vs 5.41 ± 0.33 %; $P=0.01$). In the group with TSH <2.00 μUI/ml the following correlation were significant: PTFQI with LDL cholesterol ($r=$-0.44; $P=0.04$), QUICKI with triglycerides ($r=0.48$; $P=0.02$), QUICKI with B12 vitamin ($r=0.69$; $P=0.001$) and IGI with triglycerides ($r=0.46$; $P=0.03$). In the group with TSH >2.00 μUI/ml we found significative correlation between HOMA-B and ApoA1 ($r=$-0.86; $P=0.01$).
Conclusion
In euthyroid patients with AIT, we observed significant interrelationships between thyroid function, thyroid hormone resistance, lipid profile and insulin resistance, which may contribute to increased cardiovascular risk.

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P506

A Rare Association of Thyroid Medullary Carcinoma with Paraneoplastic Cushing Syndrome: Effects of Multidisciplinary Approach

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Introduction
Medullary thyroid cancer (MTC) is a neuroendocrine tumor of the parafollicular or C cells of the thyroid gland. While thyroid cancer is increasingly common worldwide, MTC still has a low incidence. We present a case of a seventy-one-years-old woman who presented in our unit after an axillary adenopathy biopsy which tested sparsely positive for KeratinPan, CK7, CEA, TTF1, Chromogranin, Snaptophysin and calcitonin, focal positive for EMA, PAX8, Ki67 30%. Also multiple liver, lung and supraclavicular, axillary tumors were described, the largest supraclavicular adenopathy was 59/35 mm. The evaluation in our clinic, in august described a large thyroid gland with multiple nodules described in both lobes, the largest of them was bulking in the mediastinum, reaching the aortic cross and measured 3.93/3.5 cm, imprecisely delimited from the surrounding tissue, with multiple calcifications and high vascularization, as well as multiple large latherocervical lymph nodes. Calcitonin (177000 pg/ml) and CEA (305 ng/ml) where also elevated suggestive for MTC. The additional evaluation revealed a severe hypokalemia, and high cortisol and ACTH values unsuppressed after high dose Dexamethasone, suggesting associated Cushing. The patient underwent total thyroidectomy with large resection of involved lymph node

compartments, were the TNM classification was pT3b pN1b stage IV B. After hemodynamic rebalancing, and testing of the RET mutation, the patient was started on TKI, Vandetanib 200 mg/day. During one year of treatment with TKI, the patient remained stable, without any new lesions observed on the evolutive CT findings. Biochemical findings revealed an initial lowering of Calcitonin and CEA, then the values started to increase, the patient started developing cognitive impairment and dizziness. The particularity of this case high stage MTC associated with paraneoplastic Cushing make more insidious the progress and worsen prognosis of the disease, by being difficult to predict the effects of bilateral adrenalectomy, chemoembolization of liver metastases or radiofrequency ablation for lung metastases, especially in a patient with clinical decline (diarrhea, cognitive impairment, muscular weakness, dizziness which could be an indicator of disease progression-brain metastases).
Conclusions
The therapeutic approach is always a challenge in metastasized cancer, patients benefitting nowadays from the tyrosine kinase inhibitors, especially RET inhibitors, Vandetanib. The presence of distant metastases, and calcitonin doubling time are the most important prognostic factors in determining survival.
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P507

Prevalence and clinico-pathological correlations of BRAF V600E and TERT promoter mutations in differentiated thyroid cancer in Romania
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Background
Differentiated thyroid cancer (DTC) encompases a wide spectrum of disease from clinically insignificant micro-tumors to aggressive cancers. The molecular signature can be used to predict tumor behaviour, and the co-existence of BRAF and TERT promoter mutations has been identified as a marker of adverse prognosis, but we have yet no available molecular data for the Romanian population.
Objectives
To determine the prevalence of BRAF V600E and TERT promoter mutations in the Romanian thyroid cancer patients and to evaluate the association between mutational status and the clinical and pathological characteristics used in risk stratification.
Methods
We evaluated 68 tissue samples from 58 patients with DTC followed up in 'CI Parhon' Institute. Paraffin embedded tissue was used to extract genomic DNA, and BRAF V600E and C228T and C250T TERT promoter mutations were detected using Sanger sequencing.
Results
BRAF V600E mutation was present in 21.2% (11/52) patients, significantly correlated with classical papillary carcinoma and aggressive histology subtypes ($\chi2=11.29$, $P=0.023$), but not with age, invasion, TNM stage or ATA risk group. TERT promoter mutations were identified in 17.3% (9/52) of patients, and were associated with advanced age (age $\geq$45years) ($\chi2=3.352$, $P=0.06$), aggressive histological subtypes ($\chi2=9.04$, $P=0.060$) and advanced local tumor stages ($\chi2=4.121$, $P=0.042$). The patients with concomitant BRAF+TERT promoter mutations ($n=5$) presented with clinically aggressive cancer (high risk ATA) ($\chi2=6.019$, $P=0.049$), while 4/5 were radioiodine resistant.
Conclusions
We identified a low prevalence of BRAF V600E mutations, probably related to geographical (iodine deficiency) and ethnic factors, and a high prevalence of TERT promoter mutations probably due to the large proportion of aggressive cancers included. BRAF and TERT promoter mutation status helps identify patients with clinically aggressive cancer who will require intensive management.
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P508

The clinical significance of low dose biotin supplements (<300μg/day) in the treatment of patients with hypothyroidism: crucial or overestimated?
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Background
In the last decade, the combination of the widespread use of streptavidin-biotin technology and biotin–containing supplements (BCS) in the daily clinical practice, have led to numerous reports of erroneous hormone immunoassay results. However, there are no studies assessing the clinical and biochemical significance of that phenomenon, when treating patients with hypothyroidism. Therefore, a prospective study was designed to investigate the potential alterations in the measurement of thyroid hormone concentrations and clinical consequences in patients with hypothyroidism using low -dose BCS containing less than 300μg/day.
Methods
57 hypothyroid patients on thyroxine supplementation, as a result of hypothyroidism and concurrent use of BCS at a dose <300μg/day for 10 to 60 days were prospectively evaluated. Namely, TSH and free T4 (FT4) concentration measurements were performed, during BC supplementation and 10 days post BCS discontinuation and compared to 31 age-matched patients with hypothyroidism and normal thyroid hormones levels.
Results
A statistically significant increase in TSH and decline in FT4 concentrations was observed after BCS discontinuation. However, on clinical grounds, these modifications were minor and led to medication dose adjustment in only 2/57 patients (3.51%) in whom TSH was notably decreased after supplement discontinuation. Regarding the impact of biotin dose on thyroid hormone levels, no statistical significant correlation was detected between the biotin dose ingested in either TSH (r2= -0.09, $P=0.53$) or FT4 levels (r2 = 0.08, $P=0.52$). Significant increase in TSH levels was revealed only in the subgroup of patients that were taking BCS in doses > 100 μg daily
Conclusion
Our study suggests that changes in thyroid hormones profiling, due to supplements containing low dose biotin, are of minimal clinical relevance and in most cases don't hide the need to adjust the thyroxine replacement dose in patients with hypothyroidism. Larger, well-designed trials are required to further evaluate this phenomenon.
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P509

Corticosteroid therapy in dysthyroid orbitopathy: about 53 cases
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Introduction
Dysthyroid orbitopathy is an autoimmune disorder that occurs in the context of dysthyroidism. corticosteroid therapy is the main therapeutic option recommended by EUGOGO for the management of moderate and severe active forms.
Goal of the Study
Describe the clinical, para-clinical and evolutionary characteristics of dysthyroid orbitopathy treated by bolus corticosteroid therapy
Materials and Methods
This is a descriptive and analytical study including all patients with dysthyroidism associated with orbitopathy with an activity score (EUGOGO) $\geq$ 3. The protocol consists of the IV infusion of 6 boluses of 500 mg of methylprednisone per week followed by 6 others of 250 mg per week with a cumulative dose not exceeding 7.5g
Results
Our study involved 53 patients with an average age of 44.5 years. With a male predominance of 62%. The average evolution of the orbitopathy was 15.7 months. The most common etiology was Graves' disease in 96% of cases. Among our patients 18 were active smokers. The majority of patients were in biological euthyroidism. The average activity score was 4.9. In our series, 52% of patients had grade 2 proptosis and 48% had grade 3. Optic nerve damage was objectified in 6 patients. On the therapeutic level, 38 had received the entire protocol while 7 patients had interrupted before the appearance of the effects After 1 month, all the patients who had completed the protocol had reported a marked improvement with an average drop in the activity score of 3.5 which

Conclusion
Our study showed the effectiveness of corticosteroid therapy in the management of active dysthyroid orbitopathies at the cost of acceptable intolerance.

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P510

Adrenal and Lung Metastases of Papillary Thyroid Carcinoma

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Objective
Distant metastases from papillary thyroid carcinoma (PTC) are relatively rare and may be associated with a poor prognosis. Herein, we describe a case report with adrenal and lung metastasis of follicular variant of PTC in the context of the review of the literature.
Case Report
A 52-year-old male presented with complaints of swelling of his neck and cough. He had been diagnosed with multinodular goiter, obesity, pre-diabetes, and hypogonadism. Bilateral multiple pulmonary nodules were detected on thorax CT. The fluoro-deoxyglucose positron emission tomography (18F-FDG PET) revealed an extremely hyperplastic and multi nodular thyroid gland with an increased FDG uptake (SUVmax: 14.2). Increased FDG uptake was present both in pulmonary nodules (SUVmax: 2.3) and also on left adrenal gland (SUVmax: 5.8). Neck ultrasonography showed conglomerated multiple isoechoic, hypoechoic nodules with cystic degeneration and increased vascularity in both lobes. Fine needle aspiration biopsy of the dominant nodule was suspicious for follicular neoplasm with positive immuno-reactivity for TTF-1, PAX8. Magnetic resonance imaging (MRI) of the abdomen demonstrated a centrally necrotic heterogeneous left adrenal mass, measured 75x60x 80 mm. It was nonfunctioning through biochemical evaluation. Biopsy from adrenal gland was compatible with thyroid carcinoma metastasis which was strongly positive for TTF-1, PAX8, thyroglobulin and HBME-1. The patient underwent total thyroidectomy and cervical lymph node dissection. A 12 cm multifocal, follicular variant of PTC with vascular invasion was detected. Tumor invasion was detected in the right jugular vein and trachea. The patient subsequently underwent left adrenalectomy, the tumor size was 10 cm. Histopathology was consistent with metastatic follicular variant of PTC. Postoperatively, the patient was administered 150 mCi of radioactive iodine orally. Whole body scanning after 131I treatment revealed radioiodine uptake in thyroid bed and bilateral lung metastasis.
Conclusions
PTC metastasizes principally to local lymph nodes. Distant metastases are uncommon and associated with poor prognosis. Among such patients pulmonary and skeletal metastases are followed by very rare and sites like brain, kidneys, liver, adrenals, breasts, skin, eyes, and pancreas. Metastasis to adrenal gland is quite rare. Around 20 cases of TPC with adrenal metastasis have been reported to date. Here, we report a rare case of follicular variant PTC with left adrenal metastasis. The patient also had synchronous involvement of the cervical lymph nodes, trachea, right jugular vein and lung. Multidisciplinary care team coordination is essential for accurate diagnosis and treatment plan formulation.

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P511

Retrospective analysis of diagnostic and therapeutic management in thyroid cancer patients in 2019- 2021 to assess the possibility of treatment de-escalation

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Introduction
In recent years, there has been a significant increase in the detection of thyroid cancer (TC) and a number of thyroid surgeries. Both the ATA 2015 and 2022 Polish guidelines allow sparing treatment in low-risk TC, nevertheless, most patients are qualified for total thyroidectomy.
Material and method
The present study analyzed how often a TC patient opts for sparing treatment and the relationship between the size of the primary focus and risk factors on histopathological examination. The possibility of preoperative evaluation of low-risk cancer was attempted. The stage of the disease, the extent of surgery, and the occurrence of risk features on histopathological evaluation were determined.
Results
A group of 1000 TC patients diagnosed between 2019 and 2021 mainly with thyroid microcarcinoma and low-risk TC was analyzed. It was shown that there was a correlation between the diameter of the tumor infiltration on histopathological examination and the occurrence of risk features. A primary tumor size of 2 cm was defined as safe for qualification for thyroid lobectomy.
Conclusions
There is a limited willingness of low-risk TC patients to undergo lobectomy. It is therefore necessary to educate physicians and patients to convince them to undergo less extensive treatment in low-risk TC.

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Predictive factors affecting prognosis in papillary thyroid microcarcinomas

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Background
Papillary thyroid microcarcinoma (PTMC) is a papillary thyroid cancer (PTC) type with a maximum diameter of $\leq$ 10 mm. Generally, PTMCs have good prognosis and low mortality risk. However, there are cases of PTMCs showing more biologically aggressive characteristics, such as lymph node (LN) involvement and distant metastasis.
Objectives
Reveal the factors affecting the prognosis and aggressiveness of PTMCs.
Methods
Retrospectively a total of 255 patients over the age of 18 operated on thyroid, at Ondokuz Mayıs University Faculty of Medicine between June 2008 and December 2021, whose pathology results reported as PTMC (maximum tumor diameter of $\leq$ 10 mm), undergoing regular follow-ups for at least 36 months were studied. Age, gender, performed surgical procedure, pathology results, recurrence, distant and lymph node (LN) metastasis, mortality, and follow-up period, tumour histological type, microscopic variant, tumor diameter, bilaterality, focality, tumor localization, presence of capsule of the tumor, capsule invasion in the tumor, parenchymal, lymphatic, perineural, and vascular invasion, necrosis, mitosis, calcification, surgical borders were studied.
Results
The mean tumour size was 5 mm (0.1-10 mm), and multifocality was seen in 137 (53.7%) patients. Capsule invasion was observed in 23 (9%) patients. Vascular invasion was present in 5 (2%) patients, the lymphatic invasion was present in 14 (5.5%) patients, and extrathyroidal invasion was present in 2 (0.8%) patients. Metastatic cervical LN were present in 24 (9.4%) patients. Comparing patients with and without LN metastasis in terms of pathology results, it was observed that lymphatic invasion and calcification presented by the tall cell variant were significantly higher in patients with LN metastasis. In addition, tumor size was larger in those with LN metastasis. Tumor size ($P=0.004$; OR = 1.380; 95% CI = 1.106-1.722) and gender ($P=0.013$; OR:4.233; 95% CI = 1.355-13.226) were found to be the main predictive factors affecting LN metastasis, as a result of the regression analysis. It was observed that LN metastasis were more common in males than females and seen more frequently as the tumour size increased.
Conclusion
Male gender and large tumour size (cut-off 6.75 mm) were found to be the factors associated with LN metastasis. It is recommended that these factors should be considered in the treatment decision, especially in LN-negative patients, regarding

prophylactic central compartment neck dissection. In case of the distant metastasis without regional LN metastasis, further studies on molecular markers are needed.

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Epidemiology of thyroid cancer in Tunisia

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Introduction
In 2020, Thyroid cancer was responsible for 586,000 cases worldwide, ranking in 9th place in terms of incidence. It is also the most common type of cancer of the endocrine system in 2020. According to the literature, thyroid cancer have reported an increase in the incidence worldwide. However, it varies greatly from country to country. The aim of this work was to evaluate the incidence of thyroid cancer and its trend in northern Tunisia between 1990 and 2019.
Materials and Methods
The data source for this study was the population based cancer registry in Northern Tunisia 2010-2014. This registry shelter around the half of the Tunisian population. Trend analysis was performed using JoinPoint software.
Results
Between 2010 and 2014, 1226 cases of thyroid cancer were recorded in Northern Tunisia. The mean age at diagnostic was around 50 years old. The standardized incidence rate was of 1.9/100.000 for men and 6.9/100.000 for women. This cancer ranked 3rd in females and 14th in males. Papillary carcinomas and adenocarcinomas were the most common histological types. This cancer was generally diagnosed at a local stage (44.7% in men and 66.7% in women). The trend of the incidence was significantly upward between 1994 and 2014 for both genders, with a Mean Annual Percent Change of 2.6% in males and 3.1% in females ($P < 0.05$).
Conclusion
The increasing trend in the incidence of thyroid cancer may reflect improved diagnostic techniques but also overdiagnosis which constitute a problem of overtreatment.

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P514

Incident gout attack precipitated by primary hypothyroidism: a case report

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Introduction
Thyroid hormones in fluence kidney function and thereby might alter serum urate levels, a major risk factor for gouty arthritis. Previous research documented a high prevalence of elevated levels of Uric acid in primary hypothyroid patients. We present the case of an incident gout attack in a patient with primary hypothyroidism.
Case report
A 72-year-old male was hospitalized for a primary hypothyroidism complicated by a rhabdomyolysis. Laboratory examinations reveled a low serum FT4 = 3.67 pg/ml (NR 7–18) and an elevated serum TSH = 46.6 IU/l, eGFR =42. The patient was treated initially with levothyroxine 12,5 µg/day . During his hospitalization, he complained of sudden onset of throbbing pain in the right wrist, rankles and metacarpophalangeal joints in a context of apyrexia. Physical examination disclosed marked deformities of his hands, feet, and synovitis localized to his wrist and ankle on the right side. The squeeze test was positive. There was no Tophi. Serum uric acid was severely elevated 731 umol/l (180-420). Sedimentation rate was normal. Joint X-rays rule out other causes of joint inflammation. Immunological investigation was negative. The diagnosis of a gout attack was finally retained. The patient was therefore referred to rheumatology department.
Conclusion
This case illustrates an incidental gout attack that was precipitated by primary hypothyroidism in a patient who had no history of gout disease. This leads us to check regularly uric acid in patients with hypothyroidism and to check the thyroid status in patients who presents for gout attack.

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P515

Multinodular Goitre followed by a new diagnosis of PTEN Hamartoma Tumor Syndrome in an adult patient- A Case report

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Introduction
PTEN Hamartoma Tumor Syndrome (PHTS)is a rare genetic spectrum of disorders characterised by multiple hamartomas and increased risk of cancers including thyroid cancer. People with PHTS have an increased lifetime risk of differentiated thyroid carcinoma (DTC), estimated to be about 35% compared to the general population risk of below 1% (1).
Case Presentation
We report a 38-year-old male who presented with a Goitre found on routine examination present for over 2 years. Noticeably, he had unexplained mild learning difficulties and macrocephaly present since childhood. There were no risk factors for thyroid cancer on the first assessment. His thyroid function tests were normal, thyroid ultrasound USS showed a multinodular goitre with a U3 nodule and his fine needle aspiration FNA cytology was in keeping with non-neoplastic Thy2. He was also investigated for new rectal bleeding and found to have multiple bowel polyps on colonoscopy. He underwent diagnostic PTEN genetic testing and was found to have a pathogenic mosaic gene change in the PTEN gene, confirming new diagnosis of PHTS. Given the significant risk of a malignant transformation, he was discussed in the thyroid multidisciplinary team (MDT) meeting, discussing the rationale of prophylaxis thyroidectomy. A previous study favours the rationale of prophylactic thyroidectomy in certain patients with PHTS, particularly in those with developmental delay or who may struggle to adhere to screening guidelines (2). However, another study showed that patients who did not undergo a thyroidectomy also did not develop thyroid cancer during a 10-year follow-up (1). Following MDT decision, our patient underwent a prophylactic total thyroidectomy to reduce his anxiety and avoid the need for ongoing surveillance with USS & FNA.
Conclusion
It is always important to consider hereditary conditions like PHTS when evaluating patients with thyroid nodules. The need for further evaluation despite a non-neoplastic ultrasonographic and cytologic findings has to be guided based on the risk factors for thyroid cancer. Patients with PHTS are at a significantly increased risk of developing DTC and should undergo regular surveillance with consideration of prophylactic total thyroidectomy following MDT discussion.
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P516

Hyalinizing trabecular tumor of the thyroid gland. A rare entity with atypical cytological features A case report

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Introduction
Hyalinizing trabecular tumors are extremely rare and uncommon thyroid tumors, which were first described by Carney *et al*. Until now, their preoperative diagnosis based on cytological characteristics is not possible, because of the lack of specific features and molecular markers.
Case presentation
We present a 38-year-old Caucasian female, non-smoker, with a disease-free medical history, with a right-sided clearly delimited large hypoechoic thyroid lesion measuring 4.2 cm in its greatest dimension as detected by neck sonography. The patient underwent a FNAB, which showed overlapping elongated nuclei, nuclear grooves, pseudoinclusions and stromatic hyaline material between the

cell clusters. The lesion was characterized as suspicious for malignancy (Bethesda Category V). A total thyroidectomy was performed. Histologic examination confirmed a 4.2 cm encapsulated nodule on the right side of the thyroid gland. The tumor cells were polygonal to elongated with eosinophilic cytoplasm and arranged in an alveolar or trabecular pattern, while extensive hyaline material was presented at the stroma. Their nuclei exhibited nuclear grooves and pseudoinclusions. Immunohistochemical staining showed positivity for thyroid transcription factor-1, thyroglobulin and negativity for chromogranin A, calcitonin, carcinoembryonic antigen, cytokeratin 19, HBME-1. These findings were compatible with thyroid hyalinizing trabecular tumor. Treatment of hyalinizing trabecular tumors remains conservative. Patient's follow-up after thyroidectomy remains the same as the one followed after surgical removal of a thyroid neoplasm with low malignant potential.

Conclusion

Novel cytologic features including molecular panels unique for hyalinizing trabecular tumor would be of great value for pre-surgery recognition and prevention of overtreatment with thyroidectomy for treating an almost benign disease.

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P517

The relationship of Nodular Goiter Frequency and Iodine Consumption in University Students

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Nodular Goiter Disease is very common, its prevalence varies between 26 and 67%. This rate is higher in iodine deficient regions. Recent data indicate that the incidence of both benign and malignant thyroid nodules is increasing. The most important factor in noduler guatr is iodine deficiency. The reported prevalence of nodular disease depends on which population is studied and the methods used to detect the nodules. There are other risk factors that lead to an increased incidence of thyroid nodules. Some factors such as age, gender, genetics and a history of head and neck irradiation are some of these. While these factors cannot be changed, factors such as iodine deficiency, alcohol and smoking are modifiable factors for thyroid nodules. In the study we aimed to determine the frequency of nodular goiter in university students and also to investigate the relationship between the frequency of nodular goiter and dietary iodine consumption. 333 university students participated to our study who were being between the ages of 18-30 and with or without existing thyroid disease. Exclusion criteria were those with diagnosed cognitive dysfunction, pregnant and breastfeeding, odine restriction and who use drugs that could affect thyroid metabolism. Application of the research: As a result of the ultrasonographic imaging, the participants divided into those who have thyroid problems and those who do not. The presence of nodules in those with thyroid problems noted and its relationship with dietary daily iodine consumption by taking daily Food Consumption Frequency Record in both groups investigated. We also demonstrated daily amounts of fiber, some macromicronutrients and also mediterinian diet scores of all participants. We also had information about the smoking and alcohol consumption. The observeted of 333 students, the number of those with nodules is 31 (9.3%) and the number of those who do not is 302 (90.7%). Unpaired/Welch t-test and Two Sample t-test was used to determine the significance level of the relationship between numerical variables. As a result of the analysis, mean iodine consumption was higher in the group without nodules (142.17) than in the group with nodules (121.96). According to the test results, there is a significant difference as statistical between the mean differences. No relationship was found between smoking and alcohol use and the presence of nodules. No statistically significant relationship was found between fiber and the presence of nodules

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P518

Cerebral Vascular Accident in a patient presenting with a Thyroid Storm

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Thyroid storm is rare life-threatening clinical manifestation of endocrine dysfunction originating from excess level of thyroid hormone leading to hypermetabolic state with an incidence of 0.57-0.76/1000,000. The increase demand of metabolic activity subsequently induces, palpitations, dyspnoea, exercise intolerance and congestive heart failure. Most common cardiovascular manifestation of thyroid storm is tachycardia and atrial fibrillation occurs in up to 15% of patients. In very rare incidence ischemic stroke can co-occur with thyroid storm, whether it is precipitating factor or not is unclear. Without adequate treatment for both thyrotoxicosis and stroke mortality can be as high as 100%, therefore early recognition and management is essential. Herein we present a case of a patient with poorly controlled thyrotoxicosis leading to development of malignant left middle cerebral artery infarct. 58-year-old gentlemen admitted to emergency department with a sudden onset right sided weakness, facial drop, and aphasia with a NIHSS 23/42, His background is hyperthyroidism with poor compliance of medication, DVT, AF, and anaemia. On examination showed low GCS of 11 (E4V1M6), patient was able to track with eyes, no verbal response, with dense right sided weakness ongoing. CT head showed subtle hyperdensity of the left middle cerebral artery and loss of grey-white matter definition within the basal ganglia of the left cerebral hemisphere. Patient was thrombolysed and had thrombectomy, he then developed malignant MCA and underwent decompressive hemicraniectomy which led to an ITU admission where a tracheostomy was also performed. Patient was found to have thyrotoxic storm and was treated with lugols iodine, cholestyramine, iv hydrocortisone, propranolol and high dose propylthiouracil.

Discussion/Conclusion

Thyroid storm is a medical and an endocrine emergency that requires urgent management. Long standing and poorly managed thyroxicosis can cause thyrotoxicosis induced cardiomyopathy leading arrythmias including fast AF as well as heart failure. Fast AF can lead to ischaemic stroke with undesired outcome as demonstrated in this case report. This case highlights the importance of complying with the treatment for thyrotoxicosis as it can cause devastating consequences with severe life threating event with long term effect. In the light of this event, offering definitive treatment (in form of radioactive iodine or thyroidectomy) is vital in to avoid adverse or catastrophic outcome.

Test	Result	Normal value
TSH	<0.01	0.27- 4.2mU/L
T4 free	85.3	12-22pmol/l
TSH antibody	27.37	0-0.4u/ml

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P519

Aspects and Evolution of the thyroid gland in Thyroid dyshormonogenesis

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Introduction

Congenital Hypothyroidism is the principal cause of preventable mental retardation. It is due to Thyroid dysgenesis in 85% of the cases and in 15% to thyroid dyshormonogenesis.

Methods

We conducted a prospective study including 17 patients with familial congenital hypothyroidism due to thyroid dyshormonogenesis other than the features of thyroid gland by ultrasound. Other than the phenotype we evaluated the functionality by thyroid Scintigraphy with Radioactive Iodine. the mean follow up duration and the Evolution of the thyroid gland.

Results

During a long term follow up of 10,11 years [4-24] of 17 patients with congenital hypothyroidism due to thyroid dyshormonogenesis, Sex ratio was 1,83 in favor of male sex. The mean age of diagnosis was 7 year old [1 month-30 years]. Thyroid Gland size was normal in eleven patients, moderate homogenous goiter was present in five patients and One had multinodular gland Isotopic thyroid scan showed Increased Iodine Uptake with a positive perchlorate test in two patients leading to the diagnosis to TPO enzyme defect. Patients were treated with L - thyroxine normalizing TSH levels in 14 patients: baseline mean TSH was 54,92mUI/ml [5,2 -300] and Final TSH levels were 19,17[1,6-43] concomitantly, increasing volume and multinodularity was observed in three out of six patients. Regression of the Goiter was noticed in only one case. Seven out of eleven

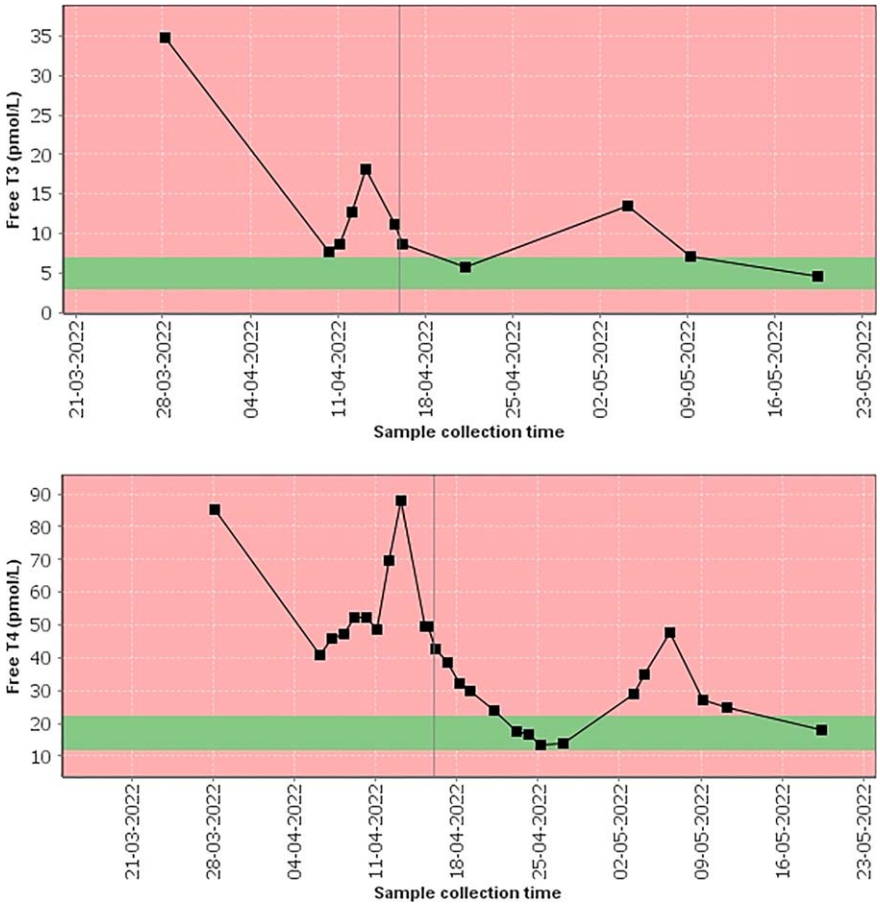

Figure 1 (Abstract P518)

patients, developed a goiter at a mean duration of 13,83 years [2-27], at a mean age 16,71 year old [3-36].

Conclusion

In our study, despite normalization of Tsh levels in our patients, increasing thyroid volume and multinodularity was observed in 52 % suggesting involving other factors than TSH in the development and differentiation of the thyroid gland.

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P520

Change in mucosal pigmentation following treatment with radioactive iodine

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Introduction

Treatment using radioactive iodine (RAI) is used in several thyroid diseases, including differentiated thyroid carcinoma (DTC). The most frequent adverse effects include acute gastrointestinal symptoms, sialadenitis, xerostomia, cervical pain, and cervical swelling. Chronic symptoms such as obstruction of the salivary ducts, pulmonary fibrosis or other primary malignant diseases are also described. A single case of change in tongue pigmentation / lingua villosa nigra following treatment with RAI for DTC, was described in a recent case report. We present a similar case of change in tongue pigmentation after treatment with RAI, also associated with nails darkening.

Case report

A 54-year-old black woman followed in our Endocrinology Department for papillary thyroid carcinoma, diagnosed at the age of 47, underwent total thyroidectomy and adjuvant treatment with 100mCi of RAI. Due to pulmonary metastasis, she was treated with a second RAI cycle of 150mCi. At that time, she was medicated with levothyroxine 125 mg/day and was asymptomatic. No relevant laboratory results were observed (hemoglobin 14.1 g/dl, leukocytes 4890x10^3/µL, platelets 374x10^3/µL, TSH $<$0.02 µUI/ml T3 139 ng/dl, antithyroglobulin antibodies $<$40 UI/ml, thyroglobulin 46.3 ng/ml). The treatment was uneventful and post-treatment body scintigraphy did not reveal any uptake, including pulmonary uptake. Two days later, she presented a striated melanonychia, discolored tongue, edema of both hands, generalized joint pain, as well as abdominal pain. These complaints spontaneously reversed over the course of two weeks. One month after the onset of symptoms, on observation, she presented on good condition, afebrile, maintaining a slight swelling of the hands and striated melanonychia on the first fingers of both hands. Her teeth were in good condition and did not presented halitosis. On the dorsal side of the tongue, a diffuse black pigmentation was observed, with discolored areas, but without fissures nor erythema. A salivary gland scintigraphy revealed severe functional and secretory impairment of the left parotid gland and a slight secretory impairment of the submandibular glands. The patient maintained a close follow-up and at the last observation, seven months after RAI treatment, her pain had improved and her tongue had a normal pigmentation, although she maintained striated melanonychia.

Conclusion

We present a case of parotid gland dysfunction associated with lingua villosa nigra as well as other unspecified symptoms, secondary to RAI, similar to a recently described case. However, striated melanonychia was also present and, to our knowledge, it is the first case describing such condition following treatment with RAI.

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P521

A case of follicular thyroid cancer in a girl with Graves' disease

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The combination of GD and FTS in children is extremely rare and is poorly understood. RSSPMC of Endocrinology named after Academician Y. Kh. Turakulov, a girl A.M., 12 years 11 months old, living in the Namangan region, was hospitalized for the purpose of diagnosis and correction of treatment. Complaints corresponded to the clinic of HT, also included bilateral protrusion of the eyeballs, lacrimation, reddening of the conjunctiva, feeling of a foreign body in the eyes, blurred vision. Anthropometry revealed severe underweight, BMI 13.9 (BMI z-score = -2.75), secondary short stature (height z-score = -1.31). Pulse 118 beats per minute, blood pressure 130/70 mm Hg. Sexual development according to Tanner 1. The thyroid gland is diffuse on palpation, enlarged to grade 2 (WHO), visible to the eye, stringy, of moderate density, mobile, painless. Peripheral lymph nodes are not palpable. Electrochemiluminescent immunoassays ECLIA from Roche Diagnostics GmbH (Germany) determined overt autoimmune HT. Ultrasound of the thyroid gland - diffuse enlargement of the thyroid gland, volume = 48mm3. Graves' disease, Graves' ophthalmopathy was diagnosed. Thyrostatic therapy was prescribed with the Tab. Thiamazole orally at a dose of 20 mg / day according to a descending scheme under the control of biochemical analyzes and instrumental examination by an endocrinologist at the place of residence. After 2 years, the girl was again admitted to our center with a relapse of GD. Palpation of the thyroid gland revealed nodes in both lobes with a diameter of up to 0.8-1.2 cm, the thyroid gland is mobile, painless, regional lymph nodes are not enlarged. TAB thyroid - Bethesda V. Preoperative preparation was carried out, after reaching euthyroidism, Lugol's solution was prescribed 8 drops 2 times a day and total thyroidectomy (TTE) was performed. Histological examination - follicular thyroid cancer. Conducted radioiodine therapy (RIT) 1200 MBC. Suppressive therapy prescribed. Levothyroxine sodium in a dose. Thyroid status is currently presented in Table 1. There are no complaints. Persistent remission.

Conclusion

GD is a rare pathology in children, FTC is diagnosed even less often. In this case, GD is more often combined with papillary TC. However, this case is an example of the coexistence of autoimmune diseases, Graves' disease, and follicular thyroid cancer in a child who required total thyroidectomy and radioiodine therapy. No matter how extremely rare the combination of GD and FTC in children is, we must remember that this is possible.

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P522

Cardiovascular health status among thyroid cancer survivors

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Background

Thyroid cancer have good global prognosis with survival rate exceeding 85% at 5 years. Survivors are exposed to higher cardiovascular morbidity and mortality than the general population. The objective of this study is to quantify the prevalence of cardiovascular health levels in an Algerian cohort of thyroid cancer survivors who were considered free of any classical cardiovascular risk factors or cardiovascular disease

Methods

A cohort of patients followed in the thyroid cancer, and not known or treated for any cardiovascular risk factor or cardiovascular disease, has been screened for cardiovascular risk factors during the period between January 2020 and June 2021. Patients have received a complete evaluated, including three measures of blood pressure, BMI, fasting blood sugar, complete lipid profile, TSH, and FT4, in addition to smoking habits. The prevalence of 6 out of 7 cardiovascular risk factors of the American Heart Association (AHA)'s cardiovascular health (CVH) have been evaluated including nonsmoking, body mass index <25 kg/m^2, physical activity, untreated total cholesterol <200 mg/dl, untreated blood pressure $<120/<80$ mm Hg, and fasting blood glucose <100 mg/dl.

Results

229 patients have been included, median age was 41 years (11-78), median time from diagnosis was 30 months (1-240), 86.5% were females, thyroid cancer type was as fellow respectively; 74%,3% and 12% for papillary, follicular, and medullary thyroid cancer. 83.3% were in stage 1 and 6.6% were in stage 2 according to AJCC 8th edition, and 6.1% had metastasis. All patients were on levothyroxine with median TSH 0.28 at mui/ml. 55.5% of patients have received radioiodine therapy. Only 16.7% have a biological or radiological persistent/recurrent disease. Cardiovascular health level was as fellow; BMI <25 in 28.7% of patients, 59.6% of patients had fasting blood glucose <100d/dl, 64.6% had total cholesterol <200 mg/dl, 33.8% had systolic blood pressure <120 mmhg, 48.1% had diastolic blood pressure <90 mmhg, and 29.2% had blood pressure $<120/<80$ mm Hg, 11% of survivors made physically active and 96.9% were not smoking. no patient had all the factors in the objective

Conclusion

In this cohort of Algerian thyroid cancer survivors, the prognosis of cancer is favorable in most cases but the achievement of cardiovascular health is far from being reached. More efforts must be implemented to improve the cardiovascular health of thyroid cancer survivors.

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P523

Primary hyperparathyroidism and papillary carcinoma of the thyroid: about a case

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Introduction

Primary hyperparathyroidism is a frequent pathology. Its association with non-medullary thyroid carcinoma is rare (2.3–4.3%). The aim of this work is to describe the particularities of this association based on an observation.

Observation

This is a 67-year-old patient who was admitted to the department for exploration of primary hyperparathyroidism discovered during a pathological fracture. Biologically she hada calcemia at 130 mg/l a parathyroid hormone at 1541 pg/l. In the morphological assessment the cervical ultrasound had objectified Presence at the level of the lower edge of the right thyroid lobe and in the extra thyroid of two nodular formations measuring respectively 12.2x11.7x11.3 mm and 18.6x 12.2x 11.5 mm suggesting two parathyroid adenomas, associated with a multi-nodular goiter whose most pejorative nodules are lower left lobe measuring 18.3x 14.5x10 mm classified EUTIRADS 4, upper right lobe measuring 9x8.5x7.1 mm, classified EUTIRAD5. A total thyroidectomy and an adenectomy were performed, with an anatomopathological examination showing the presence of a parathyroid adenoma and a papillary carcinoma of the thyroid classified as pT3b, N1a, Mx. The patient was therefore sent to the nuclear medicine department for additional treatment with radioactive iodine.

Conclusion

The association of papillary thyroid carcinoma and primary hyperparathyroidism has been reported in 2.3–4.3% of patients operated on for primary hyperparathyroidism. Our case showed underlined the interest of concomitant management of parathyroid adenomas and thyroid nodules suspicious on preoperative imaging in order to avoid surgical revision.

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P524

Anti-cancer medication related hypothyroidism: Case report

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Here we present a patient who had been on various anti-cancer medications such as tyrosine kinase inhibitors and checkpoint immune inhibitors. Eventually, anti-cancer therapy caused thyroid disfunction. Male, 74 years old, presented with fatigue, somnolence, decreased appetite, diarrhea and depression. His medications included tyrosine kinase inhibitor Axitinib (Inlyta) 5 mg which he has been taking for 1 year and human monoclonal antibody Denosumab (Exgeva) 120 mg since 2016. His family history had diabetes mellitus type 2. He has no family history of thyroid diseases. In 2012 while having routine checkup he was diagnosed with kidney cancer on the right side. He had partial right nephrectomy. However, recurrence occurred in 2015 and he had total right nephrectomy. In 2016 metastasis occurred in the right lung and bones. He was prescribed denosumab (Exgeva) and thyrosine kinase inhibitor pazopanib (Votrient) 800 mg. There was progression of the disease on the pazopanib and the patient had

palliative radiation therapy in 2018 and in 2019. From October 2019 to June 2021 he had therapy with immune checkpoint inhibitor nivolumab (Opdivo) 480 mg. He started treatment with tyrosine kinase inhibitor Axitinib (Inlyta) 5 mg in November 2021 and the dose eventually was raised to 7 mg. During presenting the patient still continued taking the axitinib 5 mg. Thyroid ultrasound showed isthmus size 2 mm, right lobe volume 5 cm^3, left lobe volume 11 cm^3, no nodules presented. The gland had heterogeneous echotexture and normal vascularity. There was no pathology in lymph nodes. The evaluation of thyroid functional tests showed TSH 39.64 μIU/ml (reference 0.35-5.6 μIU/ml), free T4 11.55 pmol/l (reference 7-20 pmol/l), free T3 4.18 pmol/l (reference 3.10-6.80 pmol/l), fasting glucose 100 mg/dl, and HbA1c 5.6%. He undergone repeated laboratory checkup the 6 days after, on 29/09/2022 in another clinic and it showed TSH 34.54 uIU/ml (reference 0.35-5.6 uIU/ml), free T3 5.26 pmol/l (reference 3.1-6.8pmol/l), free T4 10.99 pmol/l (reference 7-20 pmol/l), Ab TPO 0.1 IU/ml (reference <9 IU/ml) and Ab Tg 1 IU/ml (reference 0-4.11 IU/ml). Therapy with levo-thyroxine (L-thyroxine) 25 mg/day was started immediately and gradually raised to 50 mg/day. Since then he is maintaining improvement in his symptoms. Following oncological whole-body 18 F-Fluorodeoxyglucose (FDG) PET/BT showed metastasis in lymph node in left supraclavicular area. Axitinib 5 mg was stopped and Cabozantinib (Cabometyx) 40 mg was prescribed.

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P525

A rare association of hyperthyroidism with Darier disease: case report

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Introduction
Darier disease, also known as dyskeratosis follicularis, is a rare autosomal dominant genodermatosis characterized by a persistent eruption of keratotic papules. It is caused by mutations in the ATP2A2 gene encoding sarcoendoplasmic reticulum Ca 2+ -ATPase isoform 2 in the endoplasmic reticulum. Since it is expressed in most tissues, other organs besides the skin may be involved in Darier disease. In this case, we report a patient treated for Darier disease who was also diagnosed later with Graves disease.
Case Presentation
We report the case of a 44-year-old male patient, treated for Darier disease since the age of 13, who recently showed nervousness, irritability, weight loss and hand tremors. Initial investigation showed a hyperthyroidism which is confirmed with measurement of a suppressed serum thyrotropin concentration (TSH) at a level of 0, 17 μUI/ml, and elevated free thyroid hormones at a level of at 176 pmol/l. Physical examination showed bilateral exophthalmia, a diffuse homogeneous goiter, systolic hypertension with a blood pressure of 160/80 mmHg, and multiple hyperkeratotic papules, on the chest, upper back, forehead, scalp, nasolabial folds, and ears. Immunological investigation showed positive anti-thyroid stimulating hormone receptor antibody at the level of 41 (normal <1), and positive Thyroid peroxidase antibody (TPO) at the level of 8780 (normal<70). He was treated with two doses of radioactive Iodine-131 (10 mCi than after 7 month 17 mCi) with good evolution. After 2 months, he developed hypothyroidism and is now treated with a dose of 1,5μg/kg/day of levothyroxine.
Conclusion
In conclusion, since intracellular calcium homeostasis is of fundamental importance, Darier disease should be considered a systemic condition that requires screening for other organ dysfunctions like dysthyroidism.

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P526

Hypokalemic Thyrotoxic Periodic Paralysis. A case report

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Background
Hypokalemic Thyrotoxic Periodic Paralysis (HTPP) is a rare acquired muscular channelopathy that develops in the context of thyrotoxicosis. It consists of episodes of painless muscle weakness, precipitated by exercise, fasting, or high-carbohydrate meals. Men among ages 20-40 are more frequently affected than woman. Thyrotoxicosis (and its subsequent beta-adrenergic stimulation) increases the activation of the Sodium-Potassium ATPase channels, which leads to hyperpolarization of the muscle membrane and relative inexcitability of the muscle fibers. Peripheric insulin resistance and testosterone have also been described as contributors to the phenomenon, although the complete pathogenesis remains unclear. The degree of hypokalemia usually corresponds with the severity of clinical manifestations. We present one case of Thyrotoxic Periodic Paralysis with severe hypokalemia in the context of thyrotoxicosis.
Case description
A 23-year-old male attends the ER complaining of acute muscle weakness after an extenuating work-out prior to the visit. The symptoms progressively worsen during the night, leading to the development of tetraparesia and generalized paraesthesia. The patient refers at least three previous episodes in the last two years. Neurologic examination confirms proximal weakness in the four limbs, predominantly in lower extremities, with preserved consciousness and normal breathing pattern. Urgent laboratory test reports serum Potassium (K+) of 1.1 mEq/l. EKG shows sinus tachycardia, ST depression and frequent SV extrasystoles. Due to life-threatening risk, continuum cardiologic monitorization and intensive intravenous K+ repletion through central line is initiated in the Intensive Care Unit. After stabilization, patient confirms that he has been suffering from tachycardia, sweating, heat intolerance and distal tremor for several months. The anamnesis was negative for other symptoms or signs of hyperthyroidism. However, lab test shows supressed serum TSH (<0.005 μIU/ml) and elevated Free T4 (5.97 ng/dl), Free T3 (13.75 pg/ml) and positive Thyroid-Stimulating Immunoglobulin (TSI) (7.36 IU/l), confirming the diagnosis of Graves-Basedow Disease. Anti-thyroid medication and beta-blockers are initiated. During the evolution in hospitalization, the clinical manifestations eventually subside, accompanied by progressive normokalemia and overall clinical stability in a period of 5 days.
Conclusion
In the context of Periodic Paralysis, finding of hypokalemia must be an alert about a case of HTPP. Therefore, thyrotoxicosis should be evaluated, particularly in the absence of a family history of periodic paralysis. Monitorization and K+ supplementation must not be delayed. Restoration of euthyroidism is the only preventive measure to eliminate attacks of HTPP.

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P527

Preoperative thyroid tumor markers significance - two case reports of misleading values

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Background
Basal tumor markers are valuable in preoperative evaluation of medullary thyroid carcinoma (Calcitonin and CEA), but are insensitive and nonspecific for papilary thyroid cancer (thyroglobulin). Even if their utility is questionable or not recomended in the evaluation of thyroid nodules, in some cases refered to endocrinology department they are available and can be misleading. We present two cases of thyroid nodules with very high preoperative tumor markers.
Case 1
A 67-years old man, with history of hepatocellular carcinoma, had a markedly elevated CEA (188ng/ml; reference range <6.5ng/ml), without an evident diagnose. The calcitonin was measured and the result was 8024ng/l (<14,3ng/l). The patient was referred to endocrinology department to further investigation. The thyroid ultrassonography showed a nodule in the right lobe with 77x52x38mm predominantly solid, mildly hypoechogenic. Fine-needle aspiration was benign, immunohistochemical staining of calcitonin and CEA negative, with high calcitonin in the washout fluid (827ng/l), but incomparably lower than serum. Due to discrepancy in the results a 68Ga-DOTANOC PET was performed with high thyroid nodule uptake (SUVmax 12.6). No locoregional lymph node or distant metastasis were identified in the CT/ultrasonography. A total thyroidectomy was performed, with histological result of medullary thyroid cancer. The calcitonin 6 monts after surgery is 2.6ng/l.
Case 2
A 48-years old women presented with a hypertensive crisis with aortic dissecation. Bone metastatis were incidentally found in CT, mainly in iliac, sternum and spine. Due to non evident primary tumor, a FDG-PET was performed with abnormal uptake in a thyroid nodule (SUVmax 26), bone lesions and also in parotid gland. Thyroid function and serum thyroglobulin (Tg) levels were prescribed and the patient was referred to endocrinology department. The thyroid ultrassonography showed a 30x26x47mm predominantly solid, mildly hypoechogenic, without any suspicious lymph node. Fine-needle aspiration was non-diagnostic. Thyroid function was normal (TSH 2,17mUI/l), but Tg levels were very high (15362 mg/l; reference <77 mg/l). The bone lesions biopsy was compatible with adenocarcinoma, without expression of TTF1, PAX8 or Tg. The patient died due to disseminated intravascular coagulation, and primary tumor was not found in autopsy.

Discussion
Thyroid tumor markers are helpful in postoperative evaluation. Calcitonin is an important marker preoperatively in medullary thyroid carcinoma. However, a very high level as presented in our case isn't pathognomonic of distant metastasis. Preoperative serum Tg levels are nonspecific and can be misleading in cases of distant metastasis without evident primary tumor, as presented in our second case.

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P528

A case of Kikuchi-Fujimoto disease with fluctuating thyroid autoantibodies

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Introduction
Kikuchi-Fujimoto disease (KFD) is a benign self-limiting disease presenting with fever and lymphadenitis and mostly affecting adults younger than 40 years of age and of Asian descent. Its aetiology and pathogenesis are unknown though KFD often occurs in patients with concomitant autoimmune illness such as autoimmune thyroiditis or lupus erythematosus (SLE). We report a case of a patient with KFD and fluctuating thyroid function and thyroid autoantibody levels.
Case Report
A 35-year-old female patient presented with 4 months history of flu-like symptoms with fever, myalgia and persistent right axillary lymphadenopathy. She had past medical history of Graves' disease diagnosed at the age of 15 when she presented with clinical and biochemical thyrotoxicosis (no treatment was given at that time). Eight years later she became hypothyroid with positive anti- TPO Ab and levothyroxine was commenced at 75 mg. However, after 6 years, her TFTs showed hyperthyroid picture despite gradually reducing and then withdrawing levothyroxine (TSH $<$0.01 mU/l, Free T4 13.3 pmol/l and Free T3 2.6 pmol/l, TSH receptor antibody (TRAb) $<$0.9 U/l, Anti-TPO Ab 615 U/ml). At the time of presentation with lymphadenopathy, she was found to have slightly raised anti-dsDNA levels (51.6 IU/ml) with negative ANA, ENA, negative Crithidia dsDNA and normal ESR (20 mm/hr), TFTs 2 months before were normal. Subsequent biopsy of right axillary lymph node showed necrotizing lymphadenitis with low ki67 score. SLE and other connective tissue disorders were excluded and diagnosis of Kikuchi-Fujimoto lymphadenitis was made. Following her confirmed diagnosis of KFD, she again developed fluctuating thyroid function tests and symptoms, which were alternating between mild hypothyroidism and hyperthyroidism. Her TRAb and anti-TPO at the time were 35.6 U/l and 615 U/ml respectively. Medical treatment was not recommenced as her symptoms were mild clinically and TFTs were not significantly deranged. KFD resolved spontaneously after 3 months and there has been no recurrence since. Her TFTs and antibodies continue to fluctuate (TSH 2.43 mU/l with normal Free T4 and Free T3, thyroid stimulating immunoglobulins 0.8 IU/l and anti-TPO Ab 626 U/ml) which raises the suspicion for presence of blocking and stimulating autoantibodies.
Conclusion
KFD is a rare usually self-limiting disease with unknown aetiology; SLE and autoimmune thyroid dysfunction, especially Hashimoto's thyroiditis is often described in relation to it. Therefore, close follow up of these patients is required. The patient we report developed unusual for KFD significant fluctuations in her auto-antibodies status which are ongoing.

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P529

Myxoedma coma and NAFLD secondary to poorly controlled Hypothyrodism

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Myxoedema Coma with NAFLD secondary to poorly controlled hypothyroidism. Myxoedema coma is defined as severe hypothyroidism leading to decreased mental status, hypothermia, and other symptoms related to slowing function in multiple organs. It can culminate in severe, longstanding hypothyroidism or be precipitated by acute stressors such as infection, and surgery in patients with poorly controlled hypothyroidism. Moreover, there is a strong correlation between poorly controlled hypothyroidism and the pathogenesis of non-alcoholic fatty liver disease (NAFLD). Although the mechanism of how the two interlink remains unclear. Herein we present a case of a patient with poorly controlled hypothyroidism which caused secondary NAFLD and culminated in myxoedema coma.
Case presentation
A 79-year-old woman presented to the emergency department after being confused and less responsive at home. Her background is Hypothyroidism with poor compliance with her medication, Hypertensive, and CVA. No history of alcoholism. On presentation, her vital signs were unremarkable apart from high blood pressure of 191/112. on examination she was disoriented, physical examination was remarkable for periorbital oedema and lower limb oedema. Abdominal ultrasound showed fatty liver, CT Angiogram showed an Enlarged thyroid gland with retrosternal extension. Myxoedema coma was diagnosed, which was treated with hydrocortisone, the loading dose of levothyroxine100 micrograms followed by 50 micrograms daily with an increase of 10 micrograms till reached 100 micrograms and liothyronine 10 micrograms twice per day were given. Over 10 days patient consciousness returned to normal as well liver enzymes.
Discussion/conclusion
Myxoedema coma is a medical emergency that requires urgent management. In our case, the precipitating factor was likely poor compliance with medication for her hypothyroidism. In the case presented here patient abdominal ultrasound showed fatty liver stranding, after excluding organic and other causes of Non-Alcoholic Fatty Liver Disease it was concluded that the most probable cause of NAFLD was due to the patient's severe and poorly controlled hypothyroid. After starting Thyroxine Liver enzymes show marked improvement and return to normal levels. Based on the findings from this case we recommend screening for thyroid dysfunction in the patient that presents with non-alcoholic liver disease.

Test	Result	Normal value
Haemoglobin	108	115 – 155 g/l
ALT	814	$<$33 U/l
AST	232	$<$33 U/l
GGT	68	$<$40 U/l
Bilirubin	14	1 - 21 umol/l
TSH	$>$100	0.27 - 4.2 mU/l
Free T4	1.6	12 - 22 pmol/l
Free T3	1.8	3.1 - 6.8 pmol/l
CRP	4	$<$5 mg/l

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P530

Coexistence of thyroid nodule and Graves' disease: Is it a favorable factor for papillary thyroid cancer?

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Introduction
The incidence of papillary thyroid cancer (PTC) in the coexistence of Graves' disease (GD) and thyroid nodule is not known clearly, and the pathophysiology of PTC development in these patients is still unclear.
Aim
The aim of our study is to compare the clinicopathological features of GD patients with thyroid nodule + PTC and patients with euthyroid and non auto-immune thyroid nodule + PTC and investigate the clinicopathological features' of the patients.
Material and Method
Preoperative and postoperative clinicopathological features of 239 patients diagnosed with PTC between 2000 and 2021 were evaluated retrospectively. The patients were evaluated in 2 groups as GD+PTC and only PTC.
Results
There were 99 patients in the group with GD+PTC and 140 patients in the group with PTC without GD. The female gender was higher in the GD+PTC group.

Tumor diameter was smaller in the GD+PTC group (1,45±1,28 cm vs 1,81± 1,34 cm). Multifocal involvement was significantly less in the GD+PTC group compared to the PTC group. Among the histopathological subtypes of PTC, follicular subtype was more common in patients with non-GD PTC. Frequency of tall cell subtype was similar between two groups.
Conclusion
Malign thyroid nodules' ultrasonographic features are not different in patient with GD and PTC. In addition, presence of less multifocality and smaller tumor size in papillary carcinoma patients with Graves' disease may be considered a favorable feature.

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P531

Assessment of sleep quality in patients in remission from differentiated thyroid carcinoma: a case-control survey

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Objective
To evaluate the quality of sleep in patients in remission of differentiated thyroid cancer (DTC)
Patients and Methods
Comparative case-control study conducted at the Nuclear Medicine Center of Sfax, Tunisia including 99 individuals divided into 2 subgroups G1 ($n=39$) patients in remission from DTC G2 ($n=60$) healthy control subjects Sleep quality was assessed according to the 7 components of the Pittsburgh Sleep Quality Index (PSQI)
Results
The mean sleep period was significantly shortened in G1 patients (06H:43' vs 07H:05'; $P=0.022$). The duration of sleep in G1 patients was significantly longer than in the control group (41.5±35.4 vs 25.6±21.9 min; $P=0.035$). Subjective sleep quality (component 1), sleep latency (component 2) and sleep duration (component 3) were impaired in both groups. Sleep efficiency (component 4) is significantly lower for patients with DTC ($P=0.000$). G1 patients experience more sleep disturbances (component 5) ($P=0.000$). The use of sleeping pills (component 6) is significantly more frequent in G1. Sleep-related daytime dysfunctions (component 7) are comparable between the two groups. The global PSQI score was significantly higher in G1 (7.7±3.2 vs 5.9±2.8 points; $P=0.049$)
Discussion
Several sleep components are impaired in patients in remission from DTC compared to the general population. These patients frequently suffer from more disrupted and less compensatory sleep than normal subjects. Electro-physiological and neuro-hormonal studies are required to determine the mechanisms of these dysfunctions.

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P532

Transition from hypothyroidism to hyperthyroidism following R-CHOP treatment in mantle cell lymphoma patient

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The most common cause of primary hypothyroidism is Hashimoto's disease, while the most common cause of hyperthyroidism is Graves' disease; both conditions are autoimmune diseases. In clinical practice, the switch from hypothyroidism to hyperthyroidism is a rare phenomenon. So far, the etiology and mechanisms of conversion have not been determined. We present a case where we believe the monoclonal antibody rituximab was the primary cause of transition. A 58-year-old male patient presented to the hospital with enlarged neck lymph nodes. After undergoing a number of tests, he was diagnosed with 3 synchronous primary neoplasms: mantle cell lymphoma (B-cell lymphoma), localized colorectal cancer, and localized right kidney cancer. At the same time, he was also diagnosed with diffuse thyroid goiter and hypothyroidism (TSH 67.35 mIU/l, FT-4 3.4 pmol/l), and levothyroxine therapy was begun. First, the patient underwent surgery: a rectosigmoid colon resection and right-sided nephrectomy were performed. Due to the low grade of the lymphoma, the immunochemotherapy treatment was postponed so that the patient could receive capecitabine chemotherapy for colon cancer. At the end of capecitabine chemotherapy, the patient was euthyroid with 175 mg/day of levothyroxine, and R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride, vincristin, and prednisone) treatment for mantle cell lymphoma was started. The patient received 8 cycles of therapy within 6 months, which resulted in disease remission; however, at the end of the last cycle, the TSH values were lowered. Levothyroxine dosage was gradually reduced as a result of decreasing TSH levels, and it was completely discontinued 4 years after the end of the R-CHOP treatment. Despite discontinuation of the therapy, the patient's TSH remained <0.005 pmol/l; unfortunately, we missed levels of thyrotropin receptor antibodies (both blocking and stimulating). The patient started losing weight and had exophthalmos, therefore, thyrostatic therapy with thiamazole was started. Initially, the patient responded well to the therapy, but over time there was a relapse of hyperthyroidism, which no longer responded to thiamazole, necessitating a total thyroidectomy. Until now, nine years following the diagnosis of three primary malignant diseases, there have not been any disease relapses. There are a variety of opposing theories described in the literature about how rituximab affects the thyroid. While it is used to treat resistant Graves' orbitopathies, in our patient's case, it appears that rituximab led to the resolution of the hypothyroidism and caused the hyperthyroidism. However, it remains unclear whether chemotherapeutic agents used in combination with rituximab contributed to that transition.

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P749

A rare case of rapidly progressive Graves' orbitopathy in an elderly patient with a new-onset hyperthyroidism

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Background
Graves' orbitopathy (GO) is the major extrathyroidal manifestation of Graves' disease (GD). Even if usually mild and non-progressive, in its worst forms, GO can represent a major therapeutic challenge, because is not always responsive to the available medical treatments. First line treatment for moderate-to-severe and active GO relies on intravenous (i.v.) methylprednisolone. Optic neuropathy is a sight-threatening complication which can seriously impact the quality of life and should be immediately treated. Here we present a complicated case of worsening and aggressive GO.
Case report
In March 2022 a 78-years-old woman presented to the endocrinological outpatient clinic for newly diagnosed hyperthyroidism. Positive TSH receptor antibodies (TrAb) confirmed GD diagnosis. In medical history: atrial fibrillation on amiodarone therapy (discontinued in June 2021 because of hypothyroidism) and high blood pressure. The third dose of anti-COVID-19 vaccine was received in December 2021. During the first visit, mild ocular involvement was detected, therefore oral prednisone (25 mg per day) was prescribed together with methimazole (20 mg per day) and selenium supplementation. After 40 days, a rapid worsening of the ocular pattern occurred. The eye examination showed bilateral exophthalmos, eyelid oedema, conjunctival chemosis, with a reduced ocular motility and visual acuity. Therefore, i.v. methylprednisolone was planned, with a cumulative dose of 4.5 g in 12 weekly infusions (6 of 0.5 g plus 6 of 0.25 g). Nonetheless, after the second infusion, the orbit MRI showed diffuse hypertrophy of the oculomotor muscles with incarceration of the optic nerves. Considering the severity and evolutionary nature of the GO, in June 2022 the patient underwent urgent orbital decompression surgery, and daily 0.5 g methylprednisolone i.v. was prescribed in the perioperative days. After discharge, treatment with i.v. methylprednisolone was continued and cyclosporine (100 mg daily) was added to the treatment, with a significant clinical improvement, except for visual acuity. From August 2022, scalar therapy with oral prednisone together with ciclosporine was planned up to the maintenance dosage. The latest eye re-evaluation found in right eye only light perception and in left eye a perception of 2/30. Orthoptic rehabilitation was finally planned, although very little chance of recovery.
Conclusions
Although rare, GO can occur in acute and rapidly progressive forms, even in patients with mild hyperthyroidism and low TrAb levels at diagnosis. Since a sudden worsening can arise, GO patients should be carefully and strictly observed, hopefully in a centre equipped for multidisciplinary (both clinical and surgical) management.

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P750

Treatment Response With VRDN-001, a Full Antagonist Antibody to IGF-1 Receptor, in Thyroid Eye Disease (TED): Phase 1/2 Clinical Study

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Purpose
IGF-1R antagonism reduces TED-related inflammation and proptosis. VRDN-001, a subnanomolar affinity full antagonist antibody to IGF-1R, is being evaluated in a phase 1/2 RCT (NCT05176639) at 3-20 mg/kg. We present results from the first cohort (10 mg/kg) of TED patients.
Methods
Adults with active moderate-to-severe TED with clinical activity score (CAS) ≥ 4 were randomized to 2 infusions 3 weeks apart of either 10 mg/kg VRDN-001 or placebo (3:1). Safety, tolerability, and efficacy through 12 weeks were assessed.
Results
Baseline characteristics were similar between VRDN-001 ($n=6$) and placebo ($n=2$). At 6 weeks, overall responder rate (% of patients with ≥ 2 mm reduction in proptosis and ≥ 2 point reduction in CAS) was 83% (5/6; VRDN-001) vs. 0% (placebo); proptosis responder rate (% of patients with ≥ 2 mm reduction) was 83% (5/6; VRDN-001) vs. 50% (1/2; placebo). At 12 weeks, 80% (4/5) of VRDN-001 responders had maintained both overall and proptosis response. Mean proptosis reduction was 2.4 mm (VRDN-001) vs. 1.0 mm (placebo) at 6 weeks and remained consistent for VRDN-001 at 12 weeks (2.2 mm). MRI analysis at both 6 and 12 weeks confirmed proptosis improvement for all 4 VRDN-001 patients with scans available and showed no improvement in both placebo patients. CAS decreased to 0 or 1 for 83% (5/6; VRDN-001) vs. 0% (placebo) at 6 weeks and was maintained for 80% (4/5) at 12 weeks. Mean reduction in CAS was 4.3 (VRDN-001) vs. 1.5 (placebo) at 6 weeks and remained consistent for VRDN-001 at 12 weeks (4.2). Of the 4 VRDN-001 patients presenting with diplopia, complete resolution occurred for 3 by 6 weeks and all by 12 weeks. VRDN-001 was well-tolerated through 12 weeks. AEs were mostly mild, with no severe or serious AEs reported.
Conclusions
Two infusions of 10 mg/kg VRDN-001 were well tolerated in this cohort of TED patients, and the rapid, clinically meaningful improvement across all efficacy measures by 6 weeks was sustained through 12 weeks. These results were achieved with a lower dose and fewer treatments than in prior RCTs of other anti-IGF-1R antibodies. Results from the additional 3 mg/kg and 20 mg/kg cohorts may extend these findings and define potential VRDN-001 treatment regimens.

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P751

Thyroglobulin Point of Care Assay for Rapid Detection of Metastatic Differentiated Thyroid Carcinoma- A Pilot Study

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Introduction
Fine needle aspiration (FNA) for thyroglobulin (Tg) measurement (FNA-Tg) and for cytology (FNAC) are recommended for the evaluation of cervical lymph nodes (LN) suspected as differentiated thyroid carcinoma (DTC) metastases. LN proven to represent a metastasis of thyroid origin, change the operation plan, both prior to surgery and while encountering suspicious LN during surgery.
Aim
To assess the diagnostic accuracy of a novel point-of-care assay for Tg (POC-Tg) (PCT Patent Application No. PCT/IL2022/050067), able to detect qualitatively, within minutes, Tg in the needle washout of a suspicious LN.
Methods
Limit of detection for Tg was set at a concentration of 5 ng/ml following needle dilution with 1 mL of 0.9% saline. The POC-Tg was assessed in the FNA clinic when a LN suspected as DTC metastasis was biopsied; and in the operating room (OR) when suspicious LN was found during thyroid surgery. Each LN was evaluated using both the formal method (FNA clinic- FNAC and FNA-Tg; OR- 'frozen-section'), and the POC-Tg. Clinical decisions were made according to the formal evaluation only. The POC-Tg performance was analyzed retrospectively.
Results
FNA clinic: 22 sonographically suspicious LN were tested. Eleven were found to be positive in both our POC-Tg and the formal Tg immunoassay, with final histology reporting metastatic DTC. Ten LN were negative in both our POC-Tg and the standard Tg immunoassay, all with benign cytology. One metastatic LN, as was proven by final histology, was negative in our POC-Tg but showed low detectable Tg in the standard immunoassay.
OR
Four LNs were positive and seven negative in both our POC-Tg, and the 'frozen-section' results.
Conclusion
The diagnostic accuracy of the POC-Tg for LN metastases of DTC origin exceeded 95%, thus might change diagnostic and treatment algorithms.

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P752

A Rare Case of Covid-19 Vaccine-Associated Subacute Thyroiditis Causing Thyroid Storm

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Introduction
Subacute thyroiditis (SAT) has been reported after COVID-19 infection and SARS-CoV-2 vaccination. SAT has a mild and self-limiting course. This is the first reported case of thyroid storm following the SARS-CoV-2 vaccine
Case
A 32-year-old female patient had mild anterior neck pain, fatigue, tremor 2 weeks after being administered with the second dose of COVID-19 mRNA vaccine BNT162b2 (Pfizer–BioNTech). Initial biochemical investigations were consistent with thyrotoxicosis (Figure 1). The patient was prescribed a non-steroidal anti-inflammatory drug. After the following two weeks, she developed sweats, palpitations, hand tremor, dizziness, generalized numbness, fever, fatigue, headache and mild vomiting. The physical examination in the emergency department revealed a weak, anxious, agitated woman. She was tachycardic at 127 beats per minute, tachypneic (30 breaths per minute), and mildly hypertensive (140/95 mmHg). However, there was moderate tenderness on palpation of the anterior neck. The diagnosis of thyroid storm was made on a clinical basis according to the Burch and Wartofsky' criteria. She was hospitalized and managed by intensive monitoring, giving propranolol (40 mg$\times$4) and hydrocortisone (50 mg$\times$4, intravenous). Graves' disease couldn't be excluded completely. The sedimentation rate was moderately high (ESR: 47 mm/hr), CRP (3.23 mg)/l) was normal and there were no previously measured values. Propylthiouracil 4x50 mg/day added to treatment. At the 48th hour of the treatment, increased serum liver enzymes (ALT:375 and AST:150 U/l) were detected and antithyroid drug therapy was discontinued. However, the patient responded poorly to the treatment, her thyroid free hormone levels were very high. The patient underwent two plasma exchange procedure. There was no previous history of thyroid disease, upper respiratory tract or COVID-19 infection. She reported neck pain which is typical for subacute thyroiditis developing two weeks after vaccination. Thyroid autoantibodies were negative. Thyroid ultrasound showed diffusely enlarged gland parenchyma with a heterogeneous echotexture and decreased vascular flow. The technetium 99m scintigraphy of thyroid which was performed 4 days after the antithyroid drug discontinuation has revealed a poorly visualized thyroid gland. She was discharged home on oral steroids and a beta-blocker. The changes in her thyroid functions overtime are presented in Figure 1. The patient achieved euthyroid state 1 month after being discharged from the hospital.
Conclusions
We herein present a case of thyroid storm related to SAT -reported for the first time- following SARS-CoV-2 vaccination. Clinicians should be aware of the rare post-vaccine side effects.

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P753

Assesing the effect of thyroid dysfunction during pregnancy on maternal and neonatal outcomes with guidelines and population-based gestation-specific reference intervals

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Introduction
Adverse pregnancy outcomes have been associated with maternal thyroid dysfunction. However, optimizing the best threshold value to improve maternal and perinatal outcomes and alleviate complications by establishing population-based gestation-specific reference intervals (RIs) instead of using recommended universal cut-off values, especially for thyroid-stimulating hormone (TSH), is still an ongoing debate. The aim of this study was to compare the prevalence and risk of pregnancy outcomes based on established gestation- and laboratory-specific RIs and the recommended criteria.
Methods
We conducted a retrospective study on 2104 pregnant women in different trimesters and their infants. The national neonatal screening program was reached to obtain data on TSH measured in capillary blood. We considered TSH thresholds recommended by Endocrine Society clinical practice 2012 and revised American Thyroid Association (ATA) 2017 guidelines to classify thyroid dysfunction. In addition, trimester-specific and subgroup-specific RIs, which were based on our local population, and published previously by our group, were applied for comparison. Outcomes comprised fetal-maternal complications, including gestational hypertension, gestational diabetes mellitus (GDM), preeclampsia, preterm delivery, low birth weight (LBW $\leq$ 2500 g), and elevated neonatal TSH ($\geq$ 5.5mIU/l).
Results
Maternal hypothyroidism based on subgroup-specific classification was associated with a higher risk of GDM than was euthyroidism (2.8% vs. 7.5%; OR 2.78, 95%CI 1.01-7.62; $P=0.047$), while maternal hypothyroidism based on Endocrine Society 2012 criteria was associated with a higher risk of infants with elevated neonatal TSH (2.3% vs. 6.5%; OR 2.93, 95%CI 1.27-6.79; $P=0.012$) in the first trimester. Based on ATA 2017 guideline, trimester-specific and subgroup-specific RIs, lower median birthweight ($P=0.032$, $P=0.031$, $P=0.01$, respectively) was demonstrated in the hypothyroid women in early pregnancy compared to the euthyroid group. Among those tested in the third trimester, maternal hypothyroidism had significantly higher incidences of LBW (3.2% vs. 14.7%, $P=0.009$; 3.5% vs. 27.3, $P=0.008$; 3.6 vs. 15.4, $P=0.02$; 3.7 vs. 14.8, $P=0.025$; based on four different criteria respectively). The incidence of preterm delivery was also higher in hypothyroid women than in euthyroid women in the third trimester (7.5% vs. 20.6, $P=0.017$; 7.7% vs 23.1, $P=0.017$; 7.6% vs 22.2%, $P=0.02$; based on Endocrine Society 2012 guideline, trimester-specific and subgroup-specific RIs, respectively).
Conclusions
Our data confirmed the adverse impact of maternal thyroid function and provided further evidence for an even stronger relationship between maternal hypothyroidism and pregnancy outcomes in the case of applying different thresholds for TSH in pregnant women.

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P754

Pre-operative features of borderline thyroid lesions – outcomes of the sonographic and cytopathological analysis

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Objectives
In the 5th edition of the WHO Classification of Endocrine and Neuroendocrine Tumors thyroid tumors are divided into several new categories that allow for a clearer understanding of the cell of origin, pathologic features, molecular classification, and biological behavior. According to this classification there are some borderline nodules -the group of low-risk follicular cell-derived neoplasms - such as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), follicular tumor of uncertain malignant potential (FT-UMP) and well-differentiated tumor of uncertain malignant potential (WDT-UMP). The diagnosis is possible only postoperative based on histopathologic results. In order to raise suspicion of borderline lesions preoperatively, the outcomes of sonographic and cytopathological patterns of thyroid nodules were analysed.
Methods
In the present study we retrospectively analysed thyroid nodules of the 35 patients operated on in 2022 diagnosed with NIFTP, FT-UMP and WDT-UMP in final pathology. Sonographic features of nodules including elastography and contrast-enhanced ultrasound (CEUS) were evaluated by two experienced specialist and the risk of malignancy were assessed according to EU-TIRADS classification.
Results
Final histopathologic results included 35 thyroid nodules (in 30 women and 5 men, age ranged: 20-81, diameter range: 6-55,5mm [mean: 28.7]) diagnosed as NIFTP ($n=7$, 20%), FT-UMP ($n=21$, 60%) and WDT-UMP ($n=7$, 20%). Cytopathological results were categorised as follows: Bethesda II ($n=4$), Bethesda III ($n=2$), Bethesda IV ($n=25$), Bethesda V ($n=3$) and Bethesda VI ($n=1$). On ultrasound most of the nodules were predominantly: solid ($n=27$), ovoid shape ($n=33$), longer than tall ($n=33$), with circumscribed margins ($n=26$), mixed vascularization ($n=30$) and heterogenous echotexture ($n=15$), mildly hypoechoic ($n=16$) or isoechoic ($n=13$). The stiffness of nodules was assessed in the strain elastography either Asteria score 2 ($n=16$) or 3 ($n=11$). On CEUS examination the majority of nodules presented contrast enhanced patterns (comparing with thyroid parenchyma) as: iso- or high, heterogenous and centripetal enhancement with fast or equal wash-in and wash-out. Most lesions were classified on ultrasound as low risk - EU-TIRADS-2 ($n=13$) or intermediate risk – EU-TIRADS-3 ($n=15$), but 7 lesions were assigned to EU-TIRADS-5 characterised as taller than wide ($n=2$), markedly hypoechoic ($n=4$) with circumscribed margins ($n=2$).
Conclusions
Preliminary results indicate that most ultrasound features are typical for benign tumors, but still 20% of lesions were assigned to EU-TIRADS-5 category. Despite the fact, that borderline nodules present indolent disease with minimal risk of recurrence, it should not be underestimated, and the proper management of patients should be introduced.

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P755

Abstract withdrawn

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P756

Concordance between the ACR TIRADS ultrasound criteria, the BETHESDA cytopathology classification and final resection result in evaluation of thyroid nodules – Spanish tertiary hospital experience

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Introduction and Aims
Thyroid lesions constitute a frequent consultation in the area of endocrinology. Fine-needle aspiration (FNA) cytology is a gold standard for the evaluation of thyroid lesions, while ultrasound examination according to various thyroid imaging reporting and data system (TIRADS) criteria is gaining importance in the field. The aim of our study was to compare the sensitivity and specificity of both techniques in patients attended in thyroid lesion unit of our hospital in relation to the final resection diagnosis.
Methods
We conducted a retrospective review of lesions studied in our unit since the introduction of the ACR TIRADS criteria (2018-2021). The evaluation included cases

with Bethesda III to VI category since these had higher probability of having been operated. In the case of Bethesda III cytology a second FNA was conducted and if benign the case was labelled as benign and thus not operated. For the final analysis only the nodules with an ultrasound exam, FNA cytology and final result of histopathology (from thyroidectomy or core-needle biopsy in one case) were taken into consideration.
Results
Overall, 106 FNAs were reviewed from which 80 cases met the inclusion criteria. Out of 80 cases, 59 patients (74%) were women, and the average age was of 54 years. The risk of malignancy in presence of ACR TIRADS 3, 4, and 5 were 27%, 55% and 83% respectively and in case of Bethesda III, IV and V/VI category of 39%, 30%, and 92% respectively. To calculate sensitivity and specificity, we labelled TIRADS 2-3/Bethesda III as benign and TIRADS 4-5/Bethesda IV-VI as malignant. The overall sensitivity and specificity of ultrasound with ACR TIRADS was of 83% and 44%, and FNA of 78% and 36%.
Conclusions
Both FNA and TIRAD system showed similar trends in malignancy prediction. Ultrasound evaluation with TIRAD system demonstrated better concordance with final resection result with the exception of TIRADS 5/Bethesda V-VI group where cytological evaluation had better outcomes. Knowing the limitations of both techniques and the results of our and previous studies we consider advisable the use of both modalities adjunctively.

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68Ga-PSMA-PET vs 18F-FDG-PET in metastatic radio-refractory differentiated thyroid cancers

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Introduction
Although ^{18}F-FDG-PET has found wide application in the management of radio-refractory differentiated thyroid cancers (RAI-R-DTCs), alternative radiotracers, including ^{68}Ga-PSMA have been recently evaluated. Prostate-specific membrane antigen (PSMA) is in fact overexpressed in the microvasculature of several solid malignancies including thyroid cancers.
Aim
To compare the diagnostic performance between ^{68}Ga-PSMA-PET and ^{18}F-FDG-PET in detecting metastasis of RAI-R-DTCs
Materials and Methods
12 patients with RAI-R-DTCs underwent radiological evaluation between 2020 and 2022: in particular, CT, FDG-PET and PSMA-PET were consecutively performed over a period of no more than 6 months. The ability of FDG-PET and PSMA-PET in detecting metastases previously identified by CT was evaluated. Next, PSMA uptake (SUVmax) was compared with FDG uptake.
Results
In our population, 7 patients showed no pathological uptake, 4 patients had PET-FDG and PET-PSMA positive lesions and 1 patient had exclusively PET-FDG positive metastasis. Compared to patients without any pathological uptake, patients with PET positive lesions received an higher doses of Iodine-131 (100 vs 150 mCi, *P*-value 0.018) and showed higher thyroglobulin values at ablation (10.2 ng/ml vs 266 ng/ml, p value 0.005). A total of 42 lesions were identified by CT scan: 11 involved the lymph nodes, 17 the lungs, 8 the bones and 2 the liver. Altogether, 9 metastasis were FDG-PET positive (21.4 %), 5 were PSMA-PET positive (11.9%) of which 4 were also FDG-PET positive (9.5%). Therefore, regardless of the tracer used, no differences were found in the rate of metastases detection (9/42 - 21.4% vs 5/42 – 11.9%, *P*-value 0.24). FDG-PET positive lesions were thus subdivided: 3 in lymph nodes, 1 in lungs e 5 in bones. Only one lymph node metastasis was exclusively PSMA-PET positive, while 2 lymph node lesions and 2 bone metastasis were both FDG and PSMA-PET positive. These latter had similar SUVmax values, regardless of the tracer used and the site of the metastasis (median SUVmax values 6.2 vs 3.8 in the case of lymph node lesions and 4.8 vs 6.3 for bone metastasis with *P*-value 0.439 in both cases). None of the liver lesions were identified by PET study. Thus, there was no evidence of a different lesion distribution between the two tracers.
Conclusions
Compared to FDG-PET, PSMA-PET seems not to better detect metastasis in RAI-R-DTCs. Further prospective studies with wider populations are necessary to confirm our results.

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Cancer rate and characterstics of nodules with macrocalcification

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Aim
The aim of this study was to determine the malignant potential of thyroid nodules with macrocalcifications and to evaluate the role of other sonographic findings in the diagnosis of malignancy in thyroid nodules besides macrocalcifications.
Method
The findings of 8250 patients who applied to our outpatient clinic and underwent thyroid ultrasonography(US) between 2008 and 2021 were retrospectively reviewed. We included a total of 303 patients with 303 macrocalcified nodules (macrocalcification group) and an age- and sex matched group of 220 patients (control group) with the cytopathologic and/or histopathologic data of fine needle aspiration biopsy (FNAB) of thyroid nodules without calcification. Demographic characteristics of these patients, US characteristics of the nodules, and thyroid function tests were recorded. Cytopathological data of FNAB were classified according to BETHESDA.
Results
Overall, 458 (87.6%) of 523 nodules were benign, whereas 65 (12.4%) were malignant. When the macrocalcification and control groups were evaluated separately, 16 (7.3%) of 220 nodules in the control group were malignant, and 49 (16.2%) of 303 nodules in the macrocalcification group were malignant. Malignancy was significantly higher in the macrocalcification group than in the control group. ($P=0.002$) The nodules with macrocalcifications were divided into subgroups with peripheral interrupted calcifications and others according to the type of macrocalcification, and there was no association between peripheral interrupted calcification and malignancy risk. ($P=0.496$) We examined the sensitivity and specificity of the TI-RADS classifications. In the macrocalcification group, the sensitivity of the TIRADS classification was 54.8% (95%CI, 39.9 - 68.8%) and the specificity was 80.3% (95%CI, 74.7- 84.9%).
Conclusions
In our study, the malignancy rate was higher in the macrocalcification group than in the control group. There was no association between peripheral interrupted calcification and malignancy risk. In the macrocalcification group, the classification system TI-RADS had similar sensitivity and specificity as in the study population.
Keywords
Macrocalcification; Thyroid nodule; Ultrasonography; Thyroid cancer; TI-RADS classifications

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Redifferentiation with Vemurafenib of BRAF-mutated Radioiodine Refractory Differentiated Metastatic Thyroid Cancer in two patients

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Radioiodine treatment is the cornerstone of differentiated thyroid cancer (DTC) management. A number of thyroid cancers, however, become radioiodine-refractory (RAIR) and these represent about 60% of advanced DTCs and are responsible for the vast majority of DTC mortality. RAIR DTC has limited therapeutic options, mainly tyrosine kinase inhibitors that are associated with moderate efficacy and considerable toxicity. Reinducing NIS expression (redifferentiation) with the aim of restoring RAI avidity is a promising strategy. To this end, vemurafenib has been used in small clinical studies of BRAFV600E mutated advanced DTC with encouraging results. Two patients with RAIR, BRAFV600E mutant thyroid cancer received vemurafenib for 4 weeks. They had received a total of 400 mCi and 420 mCi ^{131}I respectively, with their latest post-therapeutic scans being negative and with progression of disease (cervical lymphadenopathy and lung metastases). After 4-week therapy with vemurafenib (960 mg BID), they both exhibited positive WBS scans and subsequently each received 200 mCi ^{131}I treatment. Both post-therapeutic WBS showed significant radioiodine uptake in the cervical neck region, and in one of the patients additional uptake in pulmonary nodules. Regarding thyroglobulin levels a different response pattern was observed in these two patients. Specifically, a significant increase in serum thyroglobulin was observed during redifferentiation treatment in one patient, whereas in the other thyroglobulin levels remained stable. Response to treatment was evaluated with imaging and serum thyroglobulin after 6 months, with both patients exhibiting stable disease, with mixed response in different metastatic areas. Vemurafenib treatment was mainly accompanied by Grade 1 or 2 adverse reactions, involving electrolyte abnormalities, skin manifestations and infections that were completely reversible. Redifferentiation reintroduces RAI in the therapeutic quiver of RAIR DTC with optimistic results avoiding the long-term adverse events of TKIs. More studies are needed to define the place of this approach in the management of advance DTC.

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Paraneoplastic Subacute Thyroiditis Secondary to Renal Cell Carcinoma

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A 52 year old lady presented with a six month history of weight loss and fatigue. Physical examination showed mild abdominal discomfort on the right flank with signs of anemia. Blood pressure was 130/60 mmHg, pulse was 83 bpm regular. Tender goitre or tremor were not present. Laboratory tests revealed tsh: 0.008 mUI/l (0.37-4.45), fT4: 2.12 ng/dl (0.8-1.8), thyroglobulin 40 ng/ml (5-42), TPO-Ab $<$35 IU/ml and TgAb $<$20 IU/ml, sedimentation:72 mm/h, crp: 59 mg/dl with normal renal, liver function test and urine dip. Previous thyroid results dated a year ago were normal. Abdominal computed tomography (CT) and thyroid ultrasound were requested. Ultrasound revealed heterogeneous echogenicity with 10 and 14 mm hyperechoic nodules on the right thyroid gland. Thyroid scan revealed a generalised decreased uptake. Abdominal CT scan revealed a 5x8 cm exophytic right renal mass with necrotic features, another 4x6,1 cm necrotic conglomerate mass which is suspicious of lymphadenopathy in the right renal hilus, pressing the right renal vein and right vena cava inferior were reported. Due to the suspicion of renal cell carcinoma (RCC), requested thorax CT showed 2.8 cm necrotic left hilar lymphadenopathy and 1 cm parenchymal nodule suspicious of metastasis in the left lingula. To assess possible paraneoplastic features, β-hcg, afp and ldh levels were measured and reported as normal. Patient was referred to the urology department for right nephrectomy and lymphadenectomy. Pathology results were consistent with stage four renal cell carcinoma. Patient was transferred to the medical oncology team for chemotherapy and follow-up. Fine-needle aspiration biopsy revealed degenerated follicular cells, multinucleated giant cells and epithelioid changes, consistent with chronic granulomatous thyroiditis. 6 weeks after the nephrectomy, thyroid functions returned to normal with tsh:0.82 mUI/l and ft4:1.78 ng/dl, which was suggestive of a subacute thyroiditis secondary to renal cell carcinoma. Literature review showed only one other similar case (1). RCC is known with its' variety of paraneoplastic features. unique inflammatory and immune-mediated responses(2). Pathophysiological role of IL-6, an inflammatory cytokine which is related to high crp levels as well, is also associated with thyroiditis as well(3).

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J – 131 therapy of autonomously functioning thyroid adenoma: the outcome of our 20 – years experience

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Objective

To investigate the results of J – 131 treatments in patients (pts) with autonomous thyroid adenomas in long period of follow up.

Material and Methods

We enrolled 68 consecutive pts with Plummer's disease (50 females, 18 males, mean age 54,7 yrs, range 21 – 79 yrs) for period 2000 – 2020 yrs. 87%(59/68) pts had a unifocal nodule, while 13% (9/68) pts had multifocal toxic autonomous nodules. Pts stopped antithyroid drugs for at least one month prior to the radioiodine therapy and than we administered a J- 131 activity of 740 -+180 MBq (range 550 – 1150 MBq), based of size and weight of 'hot' nodules and the value of radiiodine uptake. Volumetry was done by ultrasound. The mean duration of follow up was 7,84 yrs.

Results

In 65/68 (95%) pts was administered a single dose, while 3/68(5%) pts needed two doses. 62/68 (91,3%) pts who received a single dose were euthyroid with scintigraphic normalization. The percentage of euthyroid did not significantly change in long term of 20 yrs observation. The recurrent hyperthyroidism was 2,9% (2/68) pts. The cumulative incidence of hypothyroidism was 11,8% (8/68) pts withing 1 – 6,2 yrs. The nodular volume was statistically higher in pts who had recurrent hyperthyroidism over hypothyroidism ($P<0,01$) and euthyroidism ($P<0,02$). The development of hypothyroidism was higher in pts who showed extranodular uptake and after TSH suppression. No differences were observed in the results between unifocal and multifocal nodules.

Conclusions

J – 131 therapy is a simple, safe and 97% effective treatment of autonomous functioning thyroid adenoma after one or more radioiodine doses.

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Assesmement of An Artificial Intelligence-Based Decision Support System in The Thyroid Nodule Evaluation in Clinical Practice

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Objective

To evaluate the impact of a decision support system (DSS) based on artificial intelligence (AI) -KoiosDS- on ultrasound (US) image analysis and risk stratification in thyroid nodules. Material and methods Retrospective US study of all thyroid nodules with histologic (AP) result from June 2020 to December 2021. Diagnostic performance of US with ACR-TIRADS, by four endocrinologists and DSS, before and after the use of AI was evaluated.

Results

A total of 172 patients (83.1% women) with a mean age of 52.3 ± 15.3 years were evaluated. The maximum nodular diameter was 2.9 ± 1.2 cm, with 10.7% being malignant. 81.4% and 24.5% of the nodules classified by DSS as ACR-TIRADS 3 and 4, respectively, were reclassified into lower risk categories with AI When performing a ROC curve to assess the diagnostic performance of endocrinologists and DSS against the AP diagnosis, a mean increase in the area under the curve (AUC) after the use of AI was observed for endocrinologists (AUC = 0.730 vs. 0.790, $P<0.001$) and DSS (AUC = 0.696 vs. 0.735, $P<0.001$). When evaluating the impact of AI on diagnostic accuracy, we observed an improvement in mean sensitivity (S) (82.75% vs. 88%), specificity (S) (35.25% vs. 50.25%), a high negative predictive value (NPV) (94.5% vs. 96.75%) and an increase in positive predictive value (PPV) (13.5% vs. 17.75%). When analyzing the degree of agreement in the US characteristics, we observed a mean increase in concordance with the use of AI in all ultrasound patterns, especially echogenicity (kappa 0.456 vs. 0.642; $P<0.001$). As well as an improvement in the mean correlation between the endocrinologist's ACR TIRADS scores after the use of AI ($r=0.678$ vs. 0.801, $P<0.001$). When estimating the DSS as a learning tool for the endocrinologists in the first 25 image evaluated by the endocrinologist compared to the last 25, an improvement in the degree of agreement after using the AI was observed in the assessment of all the ultrasound features, particularly echogenicity (kappa 0.474 ± 0.244vs0.698 ± 0.111; $P<0.001$).

Conclusion

The use of AI in an Endocrinology Department was associated with an overall improvement in the diagnostic ability of US, as well as an increase in S, E, NPV

and PPV. AI reclassified more than half of the nodules with intermediate ACR TIRADS into lower risk categories. All US ACR-TIRADS patterns increased the degree of agreement and interindividual variability were reduced with the use of AI. AI proved to be a useful learning tool in the evaluation of thyroid nodule.

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Long term effects of 0.1 mg Recombinant Human Thyrotropin-Stimulated fix dose of radioiodine therapy in patients with recurrent multinodular goiter after surgery. A 10 year follow-up study

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Background
Several treatment options exist after thyroid malignancy has been ruled out in patients with multinodular goiter (MG). Surgery efficiently reduces the goiter size but carries a risk of both surgical and anesthetic complications while in recent years, levothyroxine suppressive therapy has been abounded. I131 therapy is the only nonsurgical alternative; however, the effectiveness diminishes with increasing goiter size and depends on iodine sufficiency in some areas. Recombinant human (rh) TSH approximately doubles the thyroid 131I uptake in patients with nodular goiter. Several studies have proved efficacy of rhTSH stimulated 131I therapy on goiter reduction.
Objective
The objective of the study was to assess the efficacy and safety of 0.1 mg rhTSH as an adjuvant to a fix dose of 131I therapy (11 mci) in patients with recurrence of large multinodular goiter several years after the initial thyrodectomy.
Patients and Intervention
14 (13 females), age 59.14 $\pm$15.44 (range 35-78 years) received 11mciu of I131, 24h after the administration of 0.1 mg rhTSH.
Main Outcome Measures
The primary endpoint was the change in thyroid volume (by ultrasound measurements) as well as in the diameter of the predominant nodule during a follow up period of 10 years. Secondary end points were the alterations in thyroid function and potential adverse effects.
Results
significant decrease in the volume of initial thyroid remnant (32.16$\pm$16.66 ml) was observed from the first reevaluation (at 4 months, 23.12$\pm$11.59 ml) as well as at the end of the follow up period (10 years, 12.62$\pm$8.76ml), $P<0.01$. There was a positive correlation between the decreased thyroid volume at 4 months with the volume of thyroid remnant at the end of the study ($r=0.407$, $P=0.014$). Significant reduction of the dominant nodule was also observed (from 31.71$\pm$10.46 mm in the beginning to 26.67$\pm$11.05 mm).
Conclusions
further investigation is needed since this approach could be attractive in terms of minimizing the potential risks of reoperation in these patient

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Microwave ablation therapy in the treatment of benign thyroid nodules: A single center experience

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Aim
Image-guided thermal ablation methods are gaining popularity in recent years for the treatment of benign and malignant thyroid nodules. It has also started to be performed more frequently in our country in the last few years, but few centers have published data on this subject. We aimed to assess the effectiveness and safeness of microwave ablation (MWA) technique in patients with benign thyroid nodules (TNs).
Materials and Methods
This retrospective and single-center study was included 72 patients with 84 benign TNs. Patients aged over 18 years old, diagnosed with USG guided fine-needle aspiration biopsy as benign by the trained pathologists about this subject, who had compression symptoms or cosmetic problems, and patients refusing surgery or at high risk for surgery were included. MWA was performed under local anesthesia. The trans-isthmic approach and moving-shot technique were used during the procedure. The pre-treatment thyroid function tests, nodule volume, cosmetic and symptom scores were compared to the 1 month follow-up. The complications were also noted.
Results
Out of 72 patients, fifty seven (79.1%) were female, and the median age was 50.31$\pm$14.26 years. The initial thyroid-stimulating hormone (TSH) and free thyroxine (T4) levels detected in the normal range before and no significant difference were found during follow-up after the ablation technique. The baseline nodule volume was 16.25 mL, and significantly decreased to 7.40 mL one month after treatment ($P<0.001$). The volume reduction rate (VRR) was 53$\pm$20% in female and 58$\pm$11% in male patients at the end of the 1st month. There was no significant difference with respect to the gender. The pretreatment mean symptom score was 7.09$\pm$1.68, and observed significant improvement after 1 month. The median cosmetic score was 3 (ranged from 1 to 4) before the procedure, and this score reduced significantly to a median of 1 (ranged from 1 to 2) after MWA ($P<0.001$). This technique was generally well-tolerated by our patients. No life-threatening major complications were observed.
Conclusions
In the treatment of benign symptomatic thyroid nodules MWA is considerable option in terms of efficacy and safety. We consider that awareness of thermal ablation methods should be increased in selected patients due to the drawbacks, need for hospitalization, risk of anesthesia, life-long L-thyroxine replacement therapy and therefore economic burden of surgery.

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An Fifty Six Gene panel Next Generation Sequencing Study of Follicular differentiated Thyroid Cancer: An Indian Study

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Background
Follicular differentiated thyroid cancer (FDTC) is the most common endocrine cancer, globally. Next-generation sequencing (NGS) in thyroid cancer allows for high-throughput genetic sequencing in short time. This analysis offers useful information on tumor biology. NGS Studies on follicular differentiated thyroid cancer are scanty from South East Asia. In this context, we set out study the pattern of a genetic panel wide somatic mutations in thyroid cancer.
Methods
We selected 20 FDTC cases. All of them underwent total thyroidectomy with neck dissection as needed. Tumour tissue samples extracted and paraffin embedded, were taken from ex-vivo specimen. Sample processing, DNA extraction, cDNA preparation and PCR amplification was performed. Mutation analysis with a thyroid cellular pathway specific 56-gene mutation panel using real-time PCR and ThyroSeq v2 on the Ion Torrent PGM sequencer was employed. Common single nucleotide polymorphisms (SNPs) with a minor allele frequency of >0.05 were excluded. Mutations were also manually checked using the Integrated Genomics Viewer v2.4.10 to filter out false positives.
Results
The analysis found mutations commonly in BRAF (16), CDKN2A (10), NRAS (6), PI3KCA (9), RET (4), RAS (12) and TP53 (3) genes. The common mutations found in the samples was RET (M918T), NRAS (Q61R), BRAF (V600E) and missense mutation in TP53 (c.217 – c.1178). A mutation has also been identified in KMT2D gene in two of the patient samples. BRAF, CDKN2A, PI3KCA were more common in papillary cancer. RAS, NRAS, RET mutations were common in follicular cancer. TP53 and KMT2D were seen only in poorly differentiated cancer.
Conclusions
NGS helps in patient management, providing risk stratification and subtyping of malignancy. It can be used in molecular tumor classification, and molecular prediction of long term outcomes in thyroid carcinoma. More prospective studies are needed for its routine use at clinical level.

Key Words
Thyroid cancer; BRAF gene; RAS gene; Genomics; Mutation
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Is it necessary to elevate TSH for FDG-PET/CT imaging in differentiated thyroid carcinoma patients with TENIS Syndrome?

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Objective
We aimed to compare the effectiveness of F-18 fluorodeoxyglucose in positron emission computed tomography (FDG-PET/CT) findings under elevated TSH levels (eTSH) and suppressed TSH levels (sTSH) in differentiated thyroid carcinoma patients with TENIS syndrome (Thyroglobulin-elevated Negative Iodine Scintigraphy).
Methods
A total of 23 patients with differentiated thyroid carcinoma (DTC) who undergone total thyroidectomy and 131I ablation therapy that presenting TENIS Syndrome were included to study. FDG-PET/CT imaging were performed to DTC patients with TENIS syndrome under two hormonal conditions: levothyroxine intake (sTSH) and hormonal withdrawal resulting TSH level $\geq$ 30 μIU (eTSH). PET/CT imaging findings were compared on the patient and lesion basis for two hormonal conditions.
Results
Positive findings were found in 15 patients with eTSH FDG-PET/CT and in 14 patients with sTSH FDG-PET/CT, and sensitivity was found as 65.2% and 60.8% for both imaging, respectively ($P > 0.05$). The number of patients who could detect a lesion with eTSH FDG-PET/CT but could not detect any lesion with sTSH FDG-PET/CT was only 1, and there was no change in the clinical management of other 14 patients. Of the total 56 lesions, 47 could be shown eTSH FDG-PET/CT, while 41 lesions could be detected with sTSH FDG-PET/CT ($P > 0.05$). Similarly, mean SUVmax values were also found to be high and not statistically significant in eTSH FDG-PET/CT imaging.
Conclusions
We concluded that eTSH FDG-PET/CT and sTSH FDG-PET/CT imaging have similar results for detecting recurrent disease in DTC patients with TENIS syndrome. On the other hand, it should be considered that eTSH FDG-PET/CT may provide some additional advantages.

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Analysis of curative effect after 131I treatment of familial differentiated thyroid cancer

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Objective
To analysis the clinical pathological characteristics and ^{131}I curative responses of familial differentiated thyroid cancer(FDTC) and sporadic differentiated thyroid cancer(SDTC).
Methods
A total of 112 FDTC patients(79 females, 33males, age(41.3 ± 15.6)) and 1000 SDTC (658 females, 342males, (44.2 ± 13.9)) who underwent ^{131}I therapy in Department of Nuclear Medicine in our hospital between January 2011 and July 2021 were retrospectively enrolled. The clinical pathological characteristics, preablative stimulated thyroglobulin (ps-Tg), preablative stimulated thyroglobulin antibody(ps-TgAb) and response to the ^{131} I therapy (excellent response, indeterminate response, biochemical incomplete response, structural incomplete response) of two groups were analyzed and compared. The clinical pathological parameters included age, gender, pathological type, tumour maximum diameter, bilateral, multifoci, nodules goiter, thyroiditis membrane invasion, lymph node metastasis(LNM), invasion of the surrounding soft tissues, distant metastasis, TNM staging and ATA risk stratification (low-risk, intermediate-risk, high-risk). χ^2test or Fisher exact test and independent-sample t test were used to compare the data between the two groups.
Results
Comparing the SDTCgroup, FDTC group showed higher proportion of bilateral foci (60.71%(68/112) *vs* 38.10%(381/1000), $\chi^2 = 10.899$, $P < 0.001$); thyroiditis membrane invasion 45.53%(51/112) *vs* 25.90%(259/1000), $\chi^2 = 9.899$, $P < 0.01$; distant metastasis:13.39%(15/112) *vs* 6.00%(6/1000). There was a ststistical difference in risk stratification between two groups (high-risk: 17.86%(20/112) *vs* 9.20%(92/1000), intermediate-risk: 67.85%(76/112) *vs* 73.00%(730/1000), low-risk: 14.28%(16/112) *vs* 17.80%(178/1000), $\chi^2 = 6.\ 989$, $P < 0.01$). The response to ^{131}I therapy of SDTC group were higher than that of the FDTC group($t = -2.275$, $P < 0.05$)There were no significant differences in other clinical pathological parameters and ps-Tg and between FDTC group and SDTC group (all $p > 0.05$). Conclusions The FDTC group displays distinct characteristics as increased aggressivess at diagnose and the worse response to ^{131}I therapy.

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Effect of Tumor Size on Prognosis in Papillary Thyroid Microcarcinoma

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Introduction
Papillary thyroid microcarcinomas (PTMC) are usually detected incidentally. They occur as a result of histological/microscopic examination of a thyroid removed especially for nodular goiter. Generally, the prognosis is good. However, it has been reported that lymph node (LN) metastasis is more common especially in PTMCs with tumor size $>$ 5mm. In this study, it was aimed to show the effect of tumor size on prognosis by comparing clinicopathological data in patients with PTMCs $\leq$ 5mm and $>$ 5mm.
Material-Method
A total of 246 patients aged $>$18 years, who were operated at Samsun Ondokuz Mayıs University Faculty of Medicine between January 2008 and October 2021 and whose pathology was reported as PTMC, were followed for at least 30 months, were included in the study. The patients were divided into two groups. The first group included 131 patients with a tumor size of $\leq$ 5mm, and the second group included 115 patients with a tumor size of 5-10mm. The age, gender, performed surgical procedure, pathology results, recurrence, distant and LN metastasis, mortality, radioactive iodine (RAI) ablation and follow-up periods were recorded. The results were compared between the two groups.
Results
When the groups were compared in terms of pathology results, multifocality ($P = 0.009$), parenchymal invasion ($P = 0.008$), calcification ($P = 0.001$), lymphatic invasion ($P = 0.002$) and presence of metastatic LN ($P < 0.001$) were found to be statistically more significant in those with tumor size $>$ 5mm. RAI ablation therapy was significantly higher in the group with tumor size $>$ 5mm ($P < 0.001$). There was no statistically significant difference between the two groups in terms of follow-up time and recurrence. Distant metastasis and disease-related death were not detected in any of them. There was a significant difference between the groups in terms of tumor type ($P = 0.049$). Tall cell variant was more common in tumor size $>$ 5mm.
Discussion and conclusion
Our findings show that recurrence rates were similar in patients with PTMCs $\leq$ 5mm and $>$5mm, and there was no disease-related mortality in either group. However, in the group with tumour size $>$ 5 mm, predictive values which may be associated with tumor aggressiveness as multifocality, parenchymal invasion, calcification, lymphatic invasion, LN metastasis and the tall cell variant were found to be significantly higher. We conclude that patients with $>$ 5mm PTMK, having these positive predictive factors, should be managed more carefully.

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P769

The Efficiency of Ultrasound Surveillance in Papillary Thyroid Cancer Patients with Excellent Response to Therapy

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Aim
To investigate the efficiency of ultrasound surveillance in detecting papillary thyroid cancer recurrences in Dynamic Risk Stratification (DRS) subgroups.
Methods
The study included 477 patients with papillary thyroid cancer (PTC) who underwent total or completion thyroidectomy and were followed for at least three ultrasound scans (US). The patients were categorized into DRS subgroups based on their first-year therapy response. The reports of consecutive US following the initial assessment were analyzed retrospectively. The US findings of the residual thyroid tissue or lymph nodes were categorized as suspicious, indeterminate, or benign based on European Thyroid Association guideline criteria. The lymph nodes that did not meet these criteria were defined as non-specific lesions. In addition, the positive predictive value (PPV) and negative predictive value (NPV) of the follow-up ultrasound scans were calculated.
Results
The median surveillance time was 76 IQR [58-104] months. Nine recurrences were observed. The recurrence rate was 0.3% in the excellent response group. The maximum time to recurrence after the first-year assessment was one year in the excellent response group (ERG) and two years in the non-excellent response group (NERG). Out of 11 fine needle aspiration biopsies performed for atypical findings in ERG, one revealed metastasis (9.1%). This ratio was 100% for the structural incomplete response group. The cumulative PPV of ERG and NERG were 1.78% and 29.76%, respectively. Given the sole recurrence in ERG subgroup was observed in the first year of assessment, the PPV of the first periodic ultrasound scans was evaluated. It was 7.69% in ERG and 34.78% in NERG.
Conclusion
The findings from the present study suggest that patients with PTC who achieved excellent response may be followed with clinical examination and serum non-stimulated thyroglobulin level.

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P770

Does targeting a TSH $\leq$ 2.5 mmol/l improve fertility in euthyroid women?

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Introduction
hypothyroidism is among the most frequent causes of infertility, our objective is to analyze this population in order to evaluate the effectiveness of treatment with levothyroxine.
Patients and methods
this is a retrospective interventional study from September 2017 to September 2022.
Inclusion criteria
infertility, TSH>2.5 mmol/l
Exclusion criteria
infertility for less than 1 year, age $\geq$ 45 years, other cause of infertility for the woman, spermogram abnormality.
Results
our work brought together 82 patients, 41% of whom presented with primary infertility, with an average age of 33 years. 32% have positive Anti TPO Abs, and 40% have a family history of thyroid disease. 33% of patients have a TSH (2.51-4.5), 51% TSH (4.51-10), 16% a TSH>10. Targeting a TSH $\leq$ 2.5 mmol/l improves the fertility rate by 56% with an average duration of 7 months under levothyroxine. There were 3 cases of abortion or stillbirth, this improvement in fertility is 48% in patients with TSH (2.51-4.5), 62% for TSH (4.51-10), 62% for TSH> 10.56% in patients with positive Anti TPO Ac, and 67% in patients with negative Anti TPO Ac.
Conclusion
our work shows that the use of levothyroxine in patients who consult for infertility with a TSH>2.5 mmol/l clearly improves fertility independently of the level of TSH and Anti-TPO Ac.

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P771

Clinical, Laboratory and Imaging Findings in the Selection of Treatment and Determination of Relapse in Subacute Thyroiditis

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Subacute Thyroiditis (SAT) is a painful, self-limited inflammation of the thyroid gland. Guidelines recommend Non-Steroid Antiinflammatory Drugs (NSAIDs) for mild cases and steroids for moderate to severe cases. Early relapses can be seen in about 9-35%. The aim of this study was to investigate the clinical, laboratory, and imaging findings that may affect treatment selection and predict relapse.
Materials and Methods
Forty SAT patients who applied to the Endocrinology and Metabolic Diseases Department of Ankara University Hospitals between Jan. 2020 – Jan. 2021 were included prospectively. All patients were evaluated with Clinical Categorical Pain Scale; NSAIDs were administered for mild cases (0-1 points) and steroids (Methylprednisolone 32 mg) for moderate to severe cases or cases unresponsive to NSAIDs. After the response, the dosage of methylprednisolone was reduced by 4 mg per 3 days. Methylprednisolone was discontinued if remission was achieved following 10 days of the 4 mg dose. If symptoms increased during or after treatment and relapse was detected, the steroid dose was increased or restarted. NSAID and steroid treatment groups at baseline and patients with and without relapse during follow-up were compared in terms of clinical, biochemical, and imaging findings.
Results
28 (70%) patients received a steroid regimen, and 12 (30%) patients received NSAIDs initially. In the steroid treatment group tenderness on palpation was more prominent (p:0,005), thyroid stimulating hormone (TSH) levels were lower (p:0.007), free T4 and free T3 levels were higher (p:0,003; 0,002), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were higher ($P<0,001$; 0,004), lymphocyte counts were lower significantly (P:0,046). The unresponsiveness to NSAIDs was 70%. The remission was achieved in 35 patients with methylprednisolone and in 2 patients with NSAIDs. Relapse was observed in 14 of 37 patients (37.8%). Only one of the relapsed patients had NSAIDs as the first-line treatment. Patients who relapsed ($n=13$) and did not relapse ($n=22$) in the steroid group were compared; ESR, and total thyroid gland volume were higher (p:0,012; 0,049) and the duration of successful treatment was longer ($P<0.001$) significantly in the relapsed group.
Conclusions
Steroids might be considered for the first-line treatment instead of NSAIDs in symptomatic patients due to the high unresponsiveness to NSAIDs. ESR and total thyroid volume might be parameters that may predict the relapse in the steroid treatment group. Slower steroid dose reduction particularly in patients with a high risk of relapse may be helpful to prevent relapse.
Keywords
Subacute Thyroiditis, Treatment, Relapse

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P772

Predictive factors for sufficient cytological result after first nondiagnostic thyroid fine-needle aspiration biopsy result

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Aim
To determine whether there is any factor that can predict sufficient results in second thyroid fine-needle aspiration biopsy (FNAB) after first nondiagnostic cytological result.
Materials and method
Nodules with non-diagnostic result after first FNAB were included and separated into two groups as sufficient (Group-1) and insufficient (Group-2) second FNAB.
Results
Second FNAB was performed on 643 nodules of 443 patients with initial nondiagnostic cytology. The result was diagnostic in 437(68.0%) nodules (Group-1) while it was again nondiagnostic in 206(32.0%) (Group-2). Thyroid autoantibody positivity were similar in groups. Cystic/mixed structure and heterogeneous echogenity were more frequent in Group-2 ($P=0.020$ and $P=0.011$, respectively). Solid structure and isoechoic appearence were more frequent in Group-1 ($P=0.003$ and $P=0.020$, respectively). Border regularity, micro/macrocalcification, taller-than-wide shape, presence of halo were comparable in two groups ($P>0.05$). There were also no significant differences

in terms of nodule dimensions, volume and rate of subcentimeter nodule between two groups($P>0.05$). In multivariate analysis, likelihood of sufficient cytology was 1.943 times higher in isoechoic nodules in comparison to heterogeneous nodules(95 CI:1.253-2.977, $P=0.003$), whereas the effect of nodule structure on sufficient result became insignificant($P=0.432$). Sufficient results group were cytologically distributed as 299 (68.4%) benign, 131 (30.0%) AUS/FLUS, 2 (0.5%) FN/SFN, 1 (0.2%) SFM and 4 (0.9%) malignant. 35 patients in Group-1 and 20 patients in Group-2 underwent thyroidectomy. Malignant histopathology was observed in 12/60(20%) nodules in Group-1 and in 3/37(8.1%) nodules in Group-2 ($P=0.116$)(Table).

Conclusions

Heterogeneous echogenity and cystic/mixt structure were more frequent in insufficient group, but after multivariate analysis, only isoechoic texture was determined to predict sufficient cytological result in rebiopsy. Second biopsy should be done to all nondiagnostic nodules because of comparable malignant histopathology results.

	Sufficient result after nondiagnostic biopsy ($n=437$, 68.0%)	**Insufficient result after nondiagnostic biopsy** (206, 32.0%)	*P*
AntiTPO positivity ($n=606$)	85 (20.6%)	28 (14.5%)	0.074
Anti-TG positivity ($n=600$)	89 (21.8%)	33 (17.3%)	0.204
Subcentimeter nodule	35 (8.0%)	18 (8.8%)	0.747
Taller-than-wider	51 (11.7%)	15 (7.3%)	0.085
Irregular border ($n=304$)	188 (89.5%)	77 (81.9%)	0.067
Echogenity ($n=587$)			**0.005**
Isoechoic	**314 (77.3%)**	118 (64.5%)	**0.001**
Hypoechoic	26 (6.4%)	18 (9.8%)	0.143
Heterogenous	66 (16.3%)	**47 (25.7%)**	**0.0071**
Nodule texture			**0.038**
solid	**404 (92.4%)**	180 (87.4%)	
cystic/mixt	33 (7.6%)	26 (12.6%)	
Microcalcification	26 (5.9%)	8 (3.9%)	0.275
Macrocalcification	36 (8.2%)	21 (10.2%)	0.415
Presence of halo	72 (16.5%)	26 (12.6%)	0.204
Histopathology, malignant ($n=97$)	12 (20.0%)	3 (8.1%)	0.116
Nodule Dimensions (mm, median (IQR))			
Anteroposterior	8.8 (7.0-12.6)	9.1 (6.8-12.8)	0.780
Lateral	11.9 (9.5-16.2)	11.8 (9.3-16.6)	0.948
Longitudinal	13.1 (10.9-19.4)	13.6 (10.7-19.1)	0.804
Nodule Volume (cm^3, median (IQR))	0.71 (0.39-2.03)	0.69 (0.37-1.91)	0.993

IQR:interquartile range

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P773

Does timing of repeat fine needle aspiration biopsy in thyroid nodules alter the adequate or AUS/FLUS cytology result?

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Aim

To determine whether early repeat fine needle aspiration biopsy(FNAB) has an effect on adequate or atypia of undetermined significance/follicular lesion of undetermined significance(AUS/FLUS) cytology rates in thyroid nodules with inadequate or AUS/FLUS in the first FNAB.

Method

Nodules of patients who underwent repeat biopsy due to insufficient or AUS/FLUS cytology between 2019-2022 were included. Demographic data of the patients and ultrasonographic, cytological and histopathological results of the nodules were recorded. Additionally, the time between the two biopsies was noted. In nodules with two FNAB results, the first was called initial, and the second was called rebiopsy. In nodules with more than two FNAB results, the time between each consecutive results was evaluated separately, and for these nodules, again first result was called initial and the second was called rebiopsy for each biopsy period of the nodule. Seven different paired groups were formed according to the time between two consecutive biopsies;before and after 1 month,45 days,2 months,3 months,6 months,9 months,12 months. The groups were compared in terms of adequate or AUS/FLUS cytological results.

Results

972 nodules of 546 patients who underwent FNAB at least twice were included. The mean age of the patients was 51 ± 12, and the female sex ratio was 79.1% ($n=432$). FNAB was performed 2 times for 573,3 times for 310, 4 times for 73, 5 times for 13 and 6 times for 3 of the nodules. A total of 2984 cytology results were evaluated. Accordingly,1026 (68.8%) of the initial biopsies were inadequate and 466 (31.2%) were AUS/FLUS. Rebiopsy results are shown in the table. There were no differences in adequate or AUS/FLUS rebiopsy results according to the different time interval groups($P>0.05$ for all). When 1026 samples with inadequate initial FNAB were considered as a separate group, to perform rebiopsy before or after any time interval had no effect on adequate or AUS/FLUS results. Similar results were obtained when a subgroup was created for samples with initial AUS/FLUS cytology($P>0.05$ for all). Also, there was no cut-off time for an adequate or AUS/FLUS rebiopsy result.

Conclusions

In patients with inadequate or AUS/FLUS initial biopsy, the rate of adequate or AUS/FLUS cytology results at rebiopsy did not vary with the timing of repeat biopsy. As recommended in the ATA guideline, there is no need to wait 3 months for a repeat biopsy. In patients with suspicious nodules in terms of malignancy, biopsy might be repeated before 1 month.

Table 1 Comparison of the parameters after patients with polycystic ovary syndrome excluded

Rebiopsy	**Initial Biopsy**			**p**
	Inadequate	**AUS/FLUS**	**Total**	<0.001
Nondiagnostic	393(38.3%)	168(36.1%)	561(37.6%)	
Benign	458(44.6%)	148(31.8%)	606(40.6%)	
AUS/FLUS	171(16.7%)	135(29.0%)	306(20.5%)	
FN/SFN	0(0.0%)	4(0.9%)	4(0.3%)	
SFM	1(0.1%)	4(0.9%)	5(0.3%)	
Malignant	3(0.3%)	7(1.5%)	10(0.7%)	
Total	1026	466	1492	

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P774

The role of oxidative stress in Hashimoto's disease

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Hashimoto disease, a chronic autoimmune lymphocytic thyroiditis, is the most common cause of hypothyroidism with a prevalence of 10–12% in the general population. Literature data suggests that persistently high levels of oxidative are considered as relevant risk factor in the occurrence and development of autoimmune diseases, including Hashimoto. The DNA and RNA are particularly valuable to the oxidative damage, and guanine is the most prone base to oxidation. Thus, the DNA/RNA repair processes are also activated by the formation of oxidants multiple guanine species, including 8-hydroxyguanosine (8-OHG), 8-hydroxy-2'-deoxyguanosine (8-OHdG), and 8-hydroxyguanine. Thus, the measurement of DNA/RNA oxidative damage, when all three oxidized guanine species; 8-hydroxy-2'-deoxyguanosine from DNA, 8-hydroxyguanosine from RNA, and 8-hydroxyguanine from either DNA or RNA would be quantify, may comprehensively determine the oxidative stress impact on nucleic acids damage and indirectly determine the level of activation of DNA/RNA repair processes. Determining the impact of oxidative stress on the development of autoimmune diseases is of great clinical importance, enabling the determination of new medical targets through the potential antioxidant implementation. Thus, the aim of the study was to evaluate the concentration of DNA/RNA oxidative stress damage products among Hashimoto's patients in comparison to healthy subjects. For the purpose of this study, 50 patients with Hashimoto disease (study group) and 30 healthy volunteers (control group) were enrolled. The DNA/RNA oxidative stress damage products were evaluated using immunoassay method. The DNA/RNA oxidative stress damage products concentration was increased among study group comparing to control group. This may lead to the Hashimoto patients' susceptibility to other diseases, including an increased risk of other autoimmune diseases or cancer. Thus, antioxidant intervention in these patients may bring many promising results, but many research in this field is still needed.

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P775

Hypothyroidism in Glycogen Storage Disease Type 1b and Management

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Glycogen storage disease (GSD) type 1 is an autosomal recessive disorder in which there is problem in glucose 6 phosphatase system. Glucose-6-phosphate transport protein deficiency is found in GSD type 1b. There is disorder in glucose metabolism, lack of glucose production in liver. Hypoglycemia, seizures, lactic acidosis, hyperuricemia and hyperlipidemia are some of the components. Affected people may also have short stature, pancytopenia and inflammatory bowel disease. Our aim is to show togetherness of GSD type 1b and autoimmune disorders. Thyroiditis and growth hormone deficiency are some examples of autoimmune disorders, in this case hypothyroidism is detected. A 22 years old woman admitted to our outpatient clinic for evaluation of primary hypothyroidism. She had a history of glycogen storage disease type 1b, Crohn's disease, rheumatoid arthritis, osteopenia, hyperuricemia and pancytopenia. Current medication is levothyroxine, filgrastim, omega-3 acid esters, allopurinol, adalimumab and glycosade. Her height is 152 cm, weight is 66 kg, hepatomegaly is detected. Her biochemical tests confirmed primary hypothyroidism. Current TSH is 7,63 mU/l, anti-thyroid peroxidase antibody 24,3 IU/ml, anti-thyroglobulin <0,9 IU/ml, uric acid 4,2 mg/dl, ALT 36 U/l, haemoglobin 10,8 g/dl, leucocyte 2780/microliter, trombocyte 105.000/microliter. Levothyroxine initiated on 2021 and dose is titrated to 100 µg in a short time and still needs further titration. Thyroid gland's parenchyma is heterogeneous but no thyroid nodule is detected on ultrasonography. Levothyroxine replacement was challenging due to difficulties in titration. The dose needed to be increased to 100 µg/day due to possible problems in absorption of the drug from the intestine. Although attention was paid to the timing of consumption of the raw corn starch, there may also have been interaction with levothyroxine. We present our case to underline the challenges of levothyroxine replacement in those patients with glycogen storage disease revealing thyroiditis and hypothyroidism.

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P776

Atezolizumab A PDL-1 Inhibitor Induced Severe Hypothyroidism Related Rhabdomyolysis

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Introduction
Recently, Programmed cell death ligand 1 (PD-L1) inhibitors have been frequently used as promising treatment options for some advanced malignancies. Although immune-related side effects secondary to PD-1 inhibitor treatment are well defined in the literature, data on PD-L1 inhibitors are limited. Thyroid dysfunction was reported in 10% of patients in the clinical study of atezolizumab. We aimed to present a case of severe hypothyroidism-related rhabdomyolysis and acute renal failure in a patient receiving atezolizumab with the diagnosis of metastatic lung cancer.
Case report
A 63-year-old male metastatic lung cancer was admitted to the hospital with complaints of generelized weakness, myalgias, shortness of breath, difficulty in walking. He has been receiving chemotherapy (carboplatin, etoposide, cisplatin) for small cell lung cancer for 2 years. Atezolizumab (PD-L1 inhibitor) was added to this treatment regimen from 3. cycle and total of 7 doses were used. The patient was receiving atezolizumab treatment every 21 days. Last dose of atezolizumab administered two weeks before admission. In the laboratory tests of the patient who did not have a known history of thyroid and kidney disease, cr: 1.6 8 mg/dl(0.7-1.2), ALT:118 U/l(<41) AST:173U/l(<40) CK: 2422 U/l (39-308), TSH: 168Mu/l(0.27-4.2), fT4: 0.3ng/l(8.9-17.1), fT3: 1,23 ng/l(2-4.4), cortisol:12.3 mg/dl (6.02-18.4) were found. In thyroid ultrasound of the patient; The thyroid gland dimensions are normal, the echo pattern is slightly heterogeneous and the echo intensity is decreased, there is no nodul. The patient was hydrated, L-thyroxine replacement was performed (excluding adrenal insufficiency). L-thyroxine treatment was gradually increased to 125 mg. After the treatment, the patient's complaints regressed. In laboratuary tests cr:1.09 mg/dl (0.7-1.2) CK:428 U/l (39-308) decreased, while TSH:63 mU/l (0.27-4.2) was suppressed, increased to fT3:2.2ng/l (2-4.4) and fT4:7.86ng/l (8.9-17.1). Liver function tests decreased to the normal range.
Conclusions
The fact that PD-L1 inhibitors cause severe hypothyroidism, rhabdomyolysis and acute kidney failure shows that the evaluation of thyroid function tests in patients using these drugs is very important. Therefore, we recommend that patients taking PD-L1 inhibitors have their thyroid function tests checked regularly and their creatinine kinase (CK) and creatinine levels should be measured when they show clinical signs of myositis such as myalgia and hypothyroidsm.
Kaynaklar
1- PD-L1 Inhibitor-Induced Thyroiditis Is Associated with Better Overall Survival in Cancer Patients. Thyroid. February 2020; 30(2): 177–184.

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P777

Rapidly-Growing Thyroid Mass: is the Diagnosis Always Anaplastic Cancer?

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A 87 year old woman admitted with complaints of hoarseness and a palpable mass which she noticed 1 week ago. She had hypothyroidism for 25 years. On examination, there was a hard and fixed palpable 4x4 cm mass on the right side of the neck. In laboratory evaluation, thyroid function tests were normal, thyroid auto-antibodies were positive, calcitonin was normal, C-reactive protein was 224 mg/l and liver and kidney function tests were normal. Thyroid ultrasonography revealed a 27.5x51.1x61.0mm isoechoic nodule containing macrocalcifications and areas of cystic degeneration completely filling the right lobe. Fine needle aspiration biopsy(FNAB) of the nodule was reported as atypia of undetermined significance. In the second FNAB;there were atypical cells with spindle cytoplasm, isolated spindle cells described in fibrin in the cell block with necrosis. The specimen was evaluated as suspicious for malignancy. Lymphoid malignancies were ruled out with flow cytometric analysis. The patient was hospitalized with a prediagnosis of anaplastic thyroid cancer. Neck MRI detected a 9.0x6.5x6.5 cm centrally necrotized mass surrounding right common carotid artery. In 18-FDG-PET-CT scanning, uptake of the lesion was significantly increased and there were multiple metastatic nodules in the lung. A tru-cut biopsy was performed. 'In cytopathologic evaluation, neoplastic infiltration consisting of fascicular shapes was observed within a fibrous stroma. Spindle cells arranged in 'herringbone pattern was observed. A large number of mitotic figures drew attention. In the immunohistochemical study, no staining was detected with TTF-1, CD34, PAX-8, CK-7, p63, SMA, desmin, FL-1, S100, synaptophysin and calcitonin. Staining with vimentin was detected. The Ki-67 proliferation index was 90%. BRAF mutation was negative.' A primary malignant fibrosarcoma of thyroid gland was considered. Because of the advanced age and poor general performance of the patient; chemotherapy and surgery were not considered. 10 sessions of radiotherapy was started. Malignant mesenchymal tumors of thyroid gland comprise 0.3% of all malignant thyroid tumours(1). Fibrosarcomas consist 9.2% of primary malignant mesenchymal tumors of thyroid(2). Although the initial diagnosis that comes to mind in a hard, fixed and rapidly-growing thyroid cancer is anaplastic cancer, malignant mesenchymal tumors like fibrosarcoma should also be considered in differential diagnosis.
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P778

Severe post-amiodarone thyrotoxicosis: personalized approach for radical treatment in a life-threatening condition

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Background
Despite increased awareness among cardiologists about the risk of amiodarone's significant side effects, it is still a commonly used antiarrhythmic drug. Amiodarone may induced easy for management hypothyroidism which affect even 25% of patients or less frequent thyrotoxicosis (AIT) which causes a challenge for clinicians. Type 1 of AIT occurs on the basis of pre-existing thyroid diseases such as nodular goiter or latent Graves' disease, type 2 results from destructive thyroiditis, and mixed/indefinite forms combine both pathomechanisms. Initial treatment of AIT includes the use of thioamides accompanied by glucocorticoids and/or perchlorate. Unfortunately, some patients refractory to this treatment may develop life-threatening symptoms. In such cases, an urgent decision must be made on salvage radical treatment. AIT induced exacerbation of cardiac insufficiency and life-threatening arrhythmias causes anaesthesia for thyroidectomy and 131-I (low 131-I uptake) therapy challenging. We aimed to assess the clinical course and results of salvage thyroidectomy or 131-I therapy in patients with life-threatening AIT refractory to medical treatment.
Materials and Methods
75 patients, hospitalized due to severe cardiac insufficiency or arrhythmias associated with AIT between 2014-2022 at a single tertiary center.
Results
In 73 of 75 patients amiodaron was withdrawn at admission. All patients received thiamazole as the best conservative treatment. Glucocorticosteroids were applied in 60, sodium perchlorate in 38, lithium carbonicum in 10 and albumins in 16 patients. The sequence of medications used depended on the individual course of the disease. In the whole group, 20 patients required salvage radical therapy due to the worsening of clinical symptoms. Six patients died during hospitalization before any radical treatment was applied. Further, 6 patients underwent total thyroidectomy. 131-I treatment was carried out in 8 cases (6 patients after rhTSH stimulation). In 4 patients a single dose of 131-I was sufficient. Four patients required repeated 131-I therapy due to thyrotoxicosis recurrence, but the partial response to first 131-I therapy enabled its repetition at the time of cardiac improvement.
Conclusion
AIT may be associated with life-threatening symptoms resulting from the exacerbation of cardiac failure and arrhythmias. The decision on the optimal time for radical AIT treatment is critical and cannot be taken too late. In selected group of patients at high risk of anaesthesia, an 131-I treatment can be considered as an effective therapeutic option. In some patients, the administration of rhTSH may be useful to improve 131-I uptake.

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P779

Autoimmune thyroid dysfunction induced by Alemtuzumab

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Background
Alemtuzumab is an anti-CD52 monoclonal antibody used in the treatment of relapsing and remitting Multiple Sclerosis (MS). It is a highly effective medication however common side effects of the treatment can include Autoimmune thyroid disease (Graves' disease, Hashimoto's thyroiditis), idiopathic thrombocytopenic purpura, anti-glomerular basement membrane disease, neutropenia, haemolytic anaemia, vitiligo being the most common presentation. This case highlights the importance of thyroid monitoring during treatment with Alemtuzumab.
Case Presentation
A 37 year old lady with a background of MS which was diagnosed in 2017, she was initially treated with IV methylprednisolone with good effect. She was then commenced as an outpatient on the Alemtuzumab, the initial course comprised five infusions in 2018 and a further three infusions were given in 2019. Following the treatment course her MS was stable. She presented to her GP in early 2022 with a picture of hyperthyroidism. Biochemical profile revealed TSH of 0.52 mU/l and T4 of 15.9 pmol/l. She was hence commenced on Carbimazole for hyperthyroidism. The GP referred her back to the Endocrinology clinic due to her background of Alemtuzumab infusions. The Carbimazole was later stopped due to hypothyroidism on repeat blood tests, at this time TSH was 62.03 mU/l. Her medications on presentation to Endocrine clinic were Carbimazole 10 mg OD, Cabergoline 0.25 mg twice a week, Sertraline, and the combined contraceptive pill. She also had a background of Macroprolactinoma on Cabergoline, this had been incidentally picked up on her initial presentation with symptoms of MS. This had been stable following commencing treatment with Dopamine agonist (Cabergoline). A DEXA scan was also performed this showed normal bone density with osteopenia of L3 and L4. On presentation with thyrotoxicosis, she has thyroid antibodies and thyroid ultrasound scan requested. The ultrasound scan showed a normal thyroid appearance, however the TSH receptor antibody levels were elevated at 61.9 U/l.
Discussion
This case report highlights the importance of regular thyroid screening in MS patients who have been treated with Alemtuzumab. In alemtuzumab-induced autoimmune thyroid dysfunction, additional challenges are posed by spontaneous, bidirectional switching between hyperthyroidism and hypothyroidism.

Set:	T3	T4	TSH
Test:	T3	T4	TSH
Units:	pmol/l	pmol/l	mU/l
Request Date			
10/11/2022 14:33	**5.4**	**15.6**	**0.13**
24/10/2022 14:42	**7.9**	**17.7**	**0.05**
17/10/2022 14:56			**0.13**
10/10/2022 14:30	**7.0**	**15.9**	**0.52**
23/06/2022 15:06	**4.0**	**9.3**	**62.03**
16/03/2022 16:10	**11.3**	**25.5**	**<0.02**
17/02/2022 18:30	**26.3**	**43.0**	**<0.02**
01/11/2021 10:07		**14.2**	**1.28**
13/01/2021 11:19	**5.5**	**14.1**	**1.72**

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P780

Thyroid and ovarian cancers occurring a decade after treated Hodgkin's disease

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Introduction
Hodgkin lymphoma is a cancer that affects the lymphatic system. Treatment includes chemotherapy and radiation therapy, which can increase the risk of secondary cancers such as thyroid and ovarian carcinomas. We report a case of a patient who developed secondary thyroid and ovarian cancers after being treated for Hodgkin's disease.
Observation
Mrs LS was diagnosed with Hodgkin disease at the age of 34 and was treated with chemotherapy and radiation therapy of the neck and supraclavicular regions, achieving full remission. Ten years later, a full-body CT scan revealed a left latero-uterine pelvic mass of the ovary, which was diagnosed as ovarian small cell carcinoma after surgery. The patient received chemotherapy as adjuvant therapy. At the age of 49, the patient consulted for a left cervical swelling. Cervical ultrasound showed a 10 mm thyroid nodule Tirads 5, with malignant cytology (Beteshda 6). The patient underwent total thyroidectomy and central lymph node dissection. Histology revealed papillary thyroid carcinoma classified as pT1aN1bMx. The patient was referred to nuclear medicine. She received a 30 mCi Radioactive Iodine Treatment. Post-therapy whole-body scan showed mild iodine uptake in the thyroid bed.
Conclusion
The patient's history of receiving radiation therapy for Hodgkin disease may have increased her risk of developing these secondary cancers. This case highlights the importance of long-term follow-up for patients treated by radiation therapy.

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P781

Quality of Life in Patients with Papillary Thyroid Cancer Assessed with The Turkish Version of The Thyroid Related Patient-Reported Outcome Questionnaire ThyPRO: A Prospective Single Center Study

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Background
Although the survival rate of papillary thyroid cancer is over 95%, the diagnosis of 'cancer' and fear of recurrence may impair the quality of life of patients. There

is no specific scale for patients with thyroid cancer, scales that can be used in the course of all chronic diseases and include the concept of general health are used to evaluate the quality of life in these patients. We aimed to evaluate the validity of the Thyroid Specific Quality of Life Scale, ThyPRO, which was developed for benign thyroid diseases, in patients with papillary thyroid cancer.
Material and Methods
121 participants who applied to Ankara University Faculty of Medicine, Department of Endocrinology and Metabolism between July 2019 and June 2021 and underwent total thyroidectomy for papillary thyroid cancer were included in this study. Patients with comorbidities were excluded from the study. In addition, the ThyPRO and SF-36 questionnaires were applied to all patients. Thyroid function tests of all patients were evaluated.
Results
A significant negative correlation was observed between the ThyPRO fatigue subscale and the SF-36 vitality subscale $r=$-0,546, $P<$0,001). When the ThyPRO anxiety, depression and emotional symptoms subscales were compared separately with the SF-36 mood subscale, significant negative correlations were found for each subscale ($r=$- 0,446, $P<$0,001; $r=$-0,403, $P<$0,001; $r=$-0,545, $P<$0,001). A significant negative correlation was observed between the ThyPRO social life subscale and the SF-36 social function subscale ($r=$-0,378, $P<$0,001). When the ThyPRO daily life subscale was compared with the SF-36 physical role and emotional role subscales, a significant negative correlation was observed ($r=$-0,413, $P<$0,001; $r=$-0,335, $P<$0,001). There was no significant correlation between the ThyPRO general quality of life assessment and SF-36 general health assessment ($P=$0,087).
Conclusions
Favorable outcomes have been observed that the ThyPRO scale can be used to evaluate the quality of life in patients followed up with papillary thyroid cancer. These findings need to be tested with a validity-reliability study in a larger patient population.

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P782

The impact of lockdown on thyroid hormone metabolism in patients on levothyroxine replacement therapy residing in Adjara

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Background
The Covid 19 pandemic has significantly changed people's lives. For patients with chronic diseases, social isolation and distancing have become a provocative factor in metabolic control disorders of varying degrees. Patients avoided hospital visits as much as possible due to fear of infection. Also for the representatives of the medical field, the pandemic has become the basis for new ways of consulting patients (remote, teleconsultation). The aim of the study was to investigate the impact of lockdown on thyroid hormone metabolism in patients on levothyroxine replacement therapy residing in Adjara (The study includes the results of two clinics)
Materials and Methods
A retrospective cohort study identified patients who underwent a dispensary at an endocrinology clinic in 2019 and 2021 due to hypothyroidism and were on replacement therapy with levothyroxine. Demographic data of patients' age, sex, and diagnosis were in the history of the disease. TSH and FT_4 level was also assessed, whether there were mid-term examinations and consultations (via social network/telemedicine service).
Results and Discussion
Data from 54 patients were reviewed as part of the study. Average 18 to 55 years, 18 males and 36 females. Of these, 38 patients were diagnosed with chronic autoimmune thyroiditis, in 16 cases with postoperative hypothyroidism. In 2019, patients's TSH ranged from 0.9- 3.2 (norm 0.5 to 5.0 mIU / L) FT_4- 0.8-1.4 (0.7 to 1.9ng / dL). Patients received levothyroxine 100 mg - 150 mg; During the pandemic period, 32 (59%) patients were examined and their thyroid status was stable (using online services), and in 8 (14.8%) cases, iatrogenic thyrotoxicosis was observed (arbitrary dose increase), 11 (20.3%) cases-hypothyroidism (decrease dose); 3 (5%) In the case of the same dose, despite the lack of control, the thyroid profile was stable.
Conclusion
The results of the study show that social isolation and distancing is a risk factors for decompensation of chronic disease, the use of online services for such patients is innovative and useful for the stability of their condition.

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P783

Antithyroid Drugs-Induced Angioedema

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Introduction
Anti-thyroid drugs like Carbimazole and Propylthiouracil are widely used in the management of hyperthyroidism. These medications are associated with a spectrum of cutaneous, hematologic, teratogenic and hepatobiliary adverse effects.
Case Report
A 65-year-old lady, known to have asthma on inhalers as needed and no history of allergies. She was diagnosed with Graves' thyrotoxicosis after she presented to her General Practitioner with mood irritability, insomnia, palpitations, and tremor of six months duration. She opted for medical therapy and was commenced on Carbimazole 30 mg per day. The patient developed lightheadedness and tongue swelling after the third dose of Carbimazole that improved with Chlorphenamine. Propylthiouracil was substituted for Carbimazole, she developed throat discomfort after the first dose and dizziness, breathing difficulty, tongue swelling and facial flushing after the second dose of the medication that required Adrenaline treatment in the Emergency Department. This case was discussed in the Endocrinology team meeting, it was felt that thyroidectomy with Potassium Iodide pre-operatively is the most appropriate treatment. She was urgently referred to our Ear, Nose and Throat surgeons and she awaits total thyroidectomy.
Conclusion
The prevalence of the antithyroid drugs-induced angioedema is unknown. While switching the patient from one anti-thyroid medication to another is the usual action in clinical practice. However, the cross-reactivity between these medications is reported to be as high as 50%. We encountered a treatment challenge in this case after the patient developed angioedema to both medications. The slow onset of disease control with radioactive iodine therapy and the risk of transient thyrotoxicosis worsening prevented us from considering this treatment option in this case.

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P784

Methimazole induced agranulocytosis - A clinical case report

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Introduction
Antithyroid drugs (ATDs) are generally safe and well tolerated, however, major side effects such as hepatotoxicity and agranulocytosis may occur and patients should be provided information on the major symptoms of these conditions. Although rare, agranulocytosis appears to be more likely with propylthiouracil (PTU) at any dose than with low-dose Methimazole (MMI).
Clinical Case
We describe the case of a 70-year-old woman referred to Endocrinology for persistent Subclinical Hyperthyroidism (SH). Her previous medical history was relevant for dyslipidemia, treated with simvastatin 40 mg, once daily. Sixteen years before, she was evaluated for diplopia and fatigue due to an unknown thyroid dysfunction and was managed with PTU, suspended due an alteration in the white blood cells. There were no other known medical conditions or allergies. On presentation to our clinic, in August 2021, she reported worsening of anxiety with no other symptoms. On examination her thyroid was not enlarged, and no signs of Graves' ophthalmopathy or fine tremors were present. A thyroid ultrasound revealed an enlarged thyroid with a 5mm cystic node. Thyroid function tests revealed low thyroid-stimulating hormone (TSH) 0.252 µUI/ml and normal free thyroxine (fT4) 1.12 ng/dl. MMI 2.5 mg daily was started for symptomatic control. After 2 months, the analytical study showed a maintenance of SH and a decrease in the white blood cell count from 3.92x10^9/l to 2.28x10^9/l. Methimazole was suspended while awaiting anti-thyroid stimulating hormone receptor antibodies (TRAbs) and thyroid scintigraphy. Six days later, the patient presented to the emergency room with a 2-day history of pharyngitis, fever, headache, nausea and vomiting. Blood tests revealed worsened leukopenia 160x10^9/l with severe neutropenia with 0 cells. Broad spectrum antibiotherapy was started. Polyclonal pANCA:AntiMPO antibodies were detected and bone marrow examination revealed severe hypocellularity with rare neutrophils.

Granulocyte-colony stimulating factor was administered for 6 days. The patient was discharged after 12 days with a normal leukocyte and neutrophil count, with the diagnosis of methimazole induced agranulocytosis.
Conclusion
A rare life-threatening side-effect of ATDs is agranulocytosis. Patients with fever or pharyngitis should seek immediate medical help. If granulocytopenia is confirmed, ATD should be suspended. Switching to the other ATD is contraindicated, because a cross-reaction between PTU and MMI has been observed. The onset of agranulocytosis is sudden and patients should be educated for warning signs at time of prescription.

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P785

Thyroid nodular disease in a patient with Neurofibromatosis type 1

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Introduction
Neurofibromatosis type 1 (NF1) is a rare autosomal dominant disease. Patients affected by NF1 have an increased risk of developing tumors other than neurofibromas, especially of endocrine origin, that's why this patients should be screened for endocrine lesions. In this report, we describe a patient affected by NF1 who present a thyroid nodule.
Observation
A 27-year-old woman was admitted in our department for endocrinological evaluations of NF1. She had a family history of NF1, primary hyperthyroidism and autoimmune diseases. The diagnosis of NF1 was made at the age of 3 months when the first skin lesions appeared on her trunk. Her follow-up was irregular. She had cervicobrachial neuralgia revealing bilateral plexiform neurofibroma in the cervical, dorsal, and lumbar region and a suspicious lateral vertebral mass regarding C6 and C7 vertebrae on spine MRI. Bilateral mammary and axillary neurofibromas are found on mammography. On fundus examination, she presented with Lisch nodules without choroidal nodules. She also suffers from chronic gastritis with duodenal polyp on esophagogastroduodenoscopy. The patient had a normal growth and puberty. She was normotensive, plasma methoxylated derivatives and phosphocalcic assessment were normal. She had a grade 1 goiter, with a normal TSH level at 2.15 mIU/l [0,25 - 4,5] and FT4 at 13,7 ng/l [9 - 18]. Anti-thyroid peroxidase and anti-thyroglobulin antibodies were negative. Cervical ultrasound showed initially a multicystic goiter. Two years later, cervical ultrasound identified one right and one left thyroid nodules respectively of 15 x 9 mm and 8 x 5 mm classified as EUTIRADS 3.
Discussion
NF1 is a common heritable neurocutaneous disorder. Central nervous system tumors, pheochromocytoma and optic nerve glioma are known to be associated with NF1. Thyroid nodular disease seems to be underestimated. In literature, there is few cases reporting the presence of thyroid neurofibroma, its possible transformation and even papillary thyroid carcinoma in patients with NF1. These finding highlight the importance of developing a guideline for the screening of thyroid diseases in these patients.

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P786

Graves' disease presented simultaneously with subacute thyroiditis - A case report

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Introduction
Graves' disease is an autoimmune disease that leads to a generalized over activity of the entire thyroid gland (*hyperthyroidism*). It is caused by TRAb thyrotropin receptor antibodies (TRAb), which bind to receptors on the surface of thyroid cells and stimulate those cells to overproduce and release thyroid hormones. **Subacute thyroiditis** is presumed to be caused by a viral infection or a postviral inflammatory process. It is a self-limited thyroid condition associated with a triphasic clinical course of hyperthyroidism, hypothyroidism, and return to normal thyroid function.
Case
In this article we present a case of a 52-years old women diagnosed with subacute thyroiditis, in the hyperthyroid phase. She was presented with fever up to 38°C, pain and tenderness on the palpation of thyroid, weakness, mild tachycardia and palpitations. Thyroid Ultrasound resulted with enlargement and heterogenous structure in both lobes, difuse hypoechoic parts with no vascularization in the right lobe, but mildly hyper vascularization in the left one. Laboratory findings: TSH = 0.005mIU/ml (n = 0.27-4.7), FT3 = 25.39pg/ml (n = 3.1-6.8), FT4 = 59.53pg/ml(n = 12-22), ESR = 72mm/h (n = 3-20), PCR = 11.15(n = 0.0-5.0), TRAb = 13.24IU/ml (n < 1.22). Covid-19 tested negative. The thyroid scan showed an enlarged gland with heterogeneous trapping. She was treated with prednisone 35 mg/d with tapering dose down to 5 mg/day in 4 weeks, beta-blocker and omeprazole. The pain and fever was resolved after 3-4 days. Four weeks later the inflammatory tests resulted negative. She was feeling much better, but she continued to have weakness. In the follow –up after 6 weeks the patient complained dyspnea. Total blood count was normal, ESR = 29 mm/h, PC r = 2.29 other renal and liver tests normal. Thoracic scan ruled out any pulmonary disease. EKG revealed tachycardia. TSH = 0.005 mIU/ml, FT4 = 100 pg/ml. The patient was started on treatment with methymasole 40 mg / day. Follow-up in 4 weeks, clinically stable, FT3 = 6.86 mIU/ml, FT4 = 17.18 mIU/ml, TRAb = 10 IU/ml, ESR = 24 mm/h, PC r = 2.0. Thyroid ultrasound continued with heterogenic structure, normal vascularization. The treatment with methymasole was tapered down to 20 mg/day. Follow up at 3 months.
Conclusions
The development of Graves' disease and subacute thyroiditis simultaneously is an uncommon condition and only a few cases have been reported. The diagnosis of Graves' disease in these patients is always difficult because of atypical signs and symptoms and the unclear onset time. The causes of the Graves' disease that followed subacute thyroiditis are still unknown. However, Graves' disease should be suspected when a high blood level of thyroid hormone and TRAb persists after subacute thyroiditis.

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P787

A rare case of autoimmune thyroiditis with frequent episodes of hashitoxicosis requiring thyroid surgery

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19 years-old female was diagnosed with thyrotoxicosis for the first time in 2015; Severe hypothyroidism developed after 1 month thiamazole therapy, therefore medication was stopped and the patient was prescribed L-T4 that resulted in improvement of thyroid function tests. L-T4 was finally withdrawn and TSH returned to normal. Since then TSH was constantly monitored and the levels were normal. In 01/2020, the patient was presented with complains about increased heart rate, emotional lability, hand tremors and oligomenorea. Lab tests revealed overt thyrotoxicosis (TSH – 0.001 mIU/ml); Additional studies, performed to clarify the genesis of thyrotoxicosis, revealed increased levels of Anti-Tg antibodies; Antibodies against TSH receptors were negative; the ultrasound of the thyroid revealed the presence of nodules in the gland, in order to clarify the diagnosis, the patient underwent a radioisotope scan of the thyroid gland, which showed decrease in uptake – 0% – consistent with destructive thyroiditis. The patient was diagnosed with transient thyrotoxicosis due to Hashimoto's thyroiditis (destructive form), which did not require pathogenic treatment, therefore, only symptomatic treatment was prescribed (beta-blocker and hydration). The studies conducted after 2 months (03/2020) were consistent with hypothyroidism (TSH – 9.5 mIU/ml, FT4 – at the lower limit of normal). She was given levothyroxine (initial dose – 25 mg); as the result thyroid hormone levels returned to normal. Since the patient has diagnosed with autoimmune thyroiditis and is being treated with levothyroxine, on the back of this, there were very frequent episodes of Hashitoxicosis (at least 6 episodes in recent years) for which it is necessary to reduce the dose of thyroxine or stop therapy completely, after which marked hypothyroidism develops soon. The patient feels thyrotoxicosis and hypothyroidism subjectively, and symptoms are disturbing for her. In addition, the patient plans pregnancy. Considering the frequent episodes of Hashitoxicosis, target level of TSH < 2.5 mIU/l according to patient's pregnancy plans and the patient's will, a shared decision was made for operative treatment – in favor of total thyroidectomy. The patient was recommended to consult a surgeon to plan total thyroidectomy. In addition, the patient has been diagnosed with polycystic ovary syndrome (hyperandrogemenia, hirsutism, oligomenorea); she is on therapy with combined oral contraceptive pills with positive result. Frequent episodes of Hashi-toxicosis with subsequent development of hypothyroidism has negative effect on reproductive system and ovarian function. So, prompt

normalization and stabilization of thyroid function tests after surgery and maintaining TSH below 2.5 mIU/ml is planned for pregnancy.

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P788

Etiological profile of hypothyroidism in transition to adult endocrinology

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Introduction

Hypothyroidism, congenital or acquired, is responsible for hypometabolism. It is the leading cause of preventable mental retardation in children. Its congenital form is common with 1 in 3500 births. The objective of our work was to describe the characteristics and etiologies of hypothyroidism.

Patients and methods

Retrospective descriptive and analytical study on patients followed for hypothyroidism in transition consultation at the department of Endocrinology and Metabolic Diseases at Ibn Rochd University Hospital in Casablanca. The statistical analysis was carried out by SPSS 25.

Results

We included 23 patients. The average age of patients was 16.6 years with a female predominance in 89% of cases. The average age of diagnosis was 3.6 years. Two patients were diagnosed in the neonatal period. A notion of consanguinity was found in 6 patients, (26% of cases). When the diagnosis was discovered, 9 patients had generalized hypotonia, 7 patients had constipation, 5 patients had delayed psychomotor acquisitions and 2 patients had respiratory disorders. Etiologically, hormone disorders were predominant in 19 patients with positive antithyroperoxidase antibodies in 11 patients. Thyroid dysgenesis was found in 4 patients. All of the patients were put on L-thyroxine with a good clinical evolution in all of our patients.

Conclusion

Hypothyroidism, in case of delayed diagnosis, can have an impact on the neurological development of the child. Hence the systematic neonatal screening and the education of parents and patients on therapeutic observance.

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P789

Treatment resistant Amiodarone-induced Thyrotoxicosis in a patient with laminopathy requiring salvage thyroidectomy

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Background

Amiodarone induced thyrotoxicosis (AIT) is a potentially catastrophic situation for patients with cardiac disease who are at risk of life-threatening complications. We describe the protracted and challenging journey of a patient with Laminopathy and a significant cardiac history who developed AIT.

Clinical Case

A 53-year-old man was referred with thyrotoxicosis (TSH <0.01mU/l, free T4 61 pmol/l, free T3 8.0 pmol/l) detected following commencement of amiodarone for atrial fibrillation. He had a history of laminopathy (due to LMNA mutation), associated cardiomyopathy and intractable arrhythmia, requiring ICD insertion, atrial and ventricular ablations. Medications included Amiodarone, Mexiletine, Bumetanide, Eplerenone, Bisoprolol, Entresto, Rivaroxaban, and Empagliflozin. Laminopathy was present in numerous relatives, including his mother, who had a history of AIT also. TRAb antibody was <0.8 IU/l. An ultrasound thyroid showed normal sized gland, mildly heterogenous echogenicity and reduced vascularity. He was treated with carbimazole and dexamethasone for AIT but remained thyrotoxic, and developed cardiac decompensation (oedema, SOB) with early myopathy. Second line agents cholestyramine and iodine solution were added, without effect. It was decided that he required salvage thyroidectomy, and he underwent numerous plasma exchanges in preparation for surgery. Following thyroidectomy, the patient recovered well. His thyroid and cardiac symptoms improved, and he was discharged on Eltroxin with follow up.

Conclusion

We describe a rare case of treatment resistant AIT. The case was complicated by the underlying laminopathy, which further increases the risk of myopathy, cardiac arrhythmia and cardiac decompensation in a thyrotoxic patient. Prompt recognition of treatment resistance is required, because the window of opportunity for safe thyroidectomy in such patients is narrow. Options for rendering patients euthyroid in resistant AIT include perchlorate, iopanoic acid, and therapeutic plasma exchange.

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P790

Unusual coexistence of primary hyperparathyroidism with graves' disease and papillary thyroid carcinoma: a case report

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Introduction

Papillary Thyroid Carcinoma (PTC) is the most frequent cancer of the thyroid. PTC may rarely coexist with Primary hyperparathyroidism (PHPT). Furthermore, the association of PTC and graves' disease (GD) has been described and the existence of a link between these entities has long been investigated, but no clear correlation has been established. We report the case of a female patient who suffered from GD, PTC and PHPT.

Observation

A 34-year-old woman consulted our endocrinology department for palpitations, tremors of the extremities and anxiety. Primary hyperthyroidism was diagnosed (TSH <0.01mUI/l, FT4 $=30$ pmol/l). It was related to Graves 'disease considering the presence of positive TSH receptor antibodies at 3.32 IU/ml. The patient was treated with Thiamazole. Furthermore, thyroid Ultrasound revealed a right thyroid nodule measuring 18*10 mm and classified as EU-Tirads 4. Fine needle aspiration was performed revealing malignant thyroid cytopathology (category VI according to the Bethesda system). Hence, surgical treatment was indicated. At the preoperative assessment, hypercalcemia was incidentally discovered (Calcemia $=$ 2,78 mmol/l) and related to a primary hyperparathyroidism (PTH $=$ 60 pg/ml). Cervical ultrasound showed a 7mm left inferior polar parathyroid adenoma, consistent with hyperfixation on parathyroid Scintigraphy. A total thyroidectomy and a left lower parathyroidectomy were performed. the final pathological examination showed a PTC classified as pT2NxMx according to TNM system.

Conclusion

The association of hyperparathyroidism with thyroid pathology has been described in the literature. Further studies are needed to clarify the link between these disorders.

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P791

Long-Term Effects of Radioiodine Treatment on Parathyroid Gland Functions in Patients with Benign or Malignant Thyroid Diseases

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Background

Radioiodine (RAI) therapy has been used for a long time in benign and malign diseases of the thyroid gland. During the application of radioiodine treatment, parathyroid glands may also be exposed to radiation due to its close proximity to the thyroid gland. There is interest in the effects of RAI treatment on parathyroid functions in clinical studies. The aim of this study is to evaluate whether the dose of RAI treatment for benign or malignant thyroid diseases has an effect on parathyroid functions in long-term follow-up or not.

Methods

The study sample consisted of 197 patients with or without receiving RAI treatment followed up for benign or malignant thyroid disease. The clinical features, preoperative and postoperative biochemical parameters and postoperative histopathological results of the patients with DTC were examined. Serum calcium, phosphorus, parathormone and 25 OH Vit d3 levels were recorded at the 3rd month, 1st year, 3rd year and 5th year after RAI treatment in all patients with or without receiving RAI treatment.

Results

A total of 197 patients, 189 of whom were diagnosed with DTC, were included in the study. 159 (80.7%) of the patients were female and 38 (19.3%) were male. The mean age at diagnosis was 43 ± 13.4 years. Total thyroidectomy was performed in 179 patients with the diagnosis of DTC and in 6 patients with Graves' disease. While the PTH levels measured in the preoperative period were higher ($P=0.002$) in 92 patients who received RAI treatment at doses of 100 mci and above, the calcium and PTH levels measured after the 1st year of RAI treatment

were found to be lower ($P=0,020$, $P=0.031$). When the patients at 5-years of follow-up after RAI treatment were evaluated, no statistically significant differences were found in terms of serum calcium, phosphorus, parathormone and 25ohvitd3 levels. However, it was found that normocalcemic hyperparathyroidism developed at ten years of follow-up in 2 patients who were treated with RAI.

Conclusions

Although the effect of RAI treatment for thyroid diseases on parathyroid functions seem to be safe in long term follow-up, normocalcemic primary hyperparathyroidism was detected in 2 patients. For this reason, before RAI treatment, patients should be informed about the potential risk of developing abnormal parathyroid function in the future. In addition, patients should be followed-up periodically to control parathyroid function after RAI treatment. Patients should be followed up for low PTH and calcium in the early period and for hyperparathyroidism in the long term.

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P792

Plasma Lipoprotein(a) Is Not Associated With Graves' Ophthalmopathy

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Aim

To investigate the relation of serum lipoprotein (a) (Lp(a)) and other serum lipids with presence of Graves' Ophthalmopathy (GO). We also analyzed the correlation between serum lipids and GO activity.

Methods

A cross-sectional investigation was conducted in consecutive patients with Graves' Disease (GD) who came under the authors' observation to receive antithyroid drug. A stratification was aimed at forming two distinct groups of patients under the same conditions concerning age, gender, alcohol consumption, and smoking. A total of 99 patients, 45 with GO and 54 without GO were included along with 56 HCs. Ophthalmological assessments and serum lipids measurements were performed.

Results

The study groups were similar in age, sex, body mass index, alcohol consumption, and smoking status. The patients without GO had the highest serum Lp(a) (6.7 mg/dl, IQR [3.7-9.9]), followed by patients with GO (5.7 mg/dl, IQR [4.3-9.2]), and HCs (4.7 mg/dl, IQR [3-7.6]). Inter-group comparisons of serum Lp(a) yielded no significant results ($P=0.165$). Serum levels of total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides also did not show any difference between patients with GO, patients without GO, and HCs ($P>0.05$ for all). Serum Lp(a), total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides were not correlated with GO activity ($P>0.05$ for all).

Conclusion

The results of this study indicated no relation of serum Lp(a), total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides with the presence of GO. Further studies with a larger sample size are needed to investigate whether the presence and activity of GO are affected by serum Lp(a) and/or other lipids.

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P793

Blood ethylenethiourea and disorders of the thyroid gland in Indian mango plantation workers

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Introduction

A suspected human carcinogen and antithyroid substance, ethylenethiourea (ETU), is produced during the metabolism of ethylenebisdithiocarbamates (EBDCs). These fungicides are sprayed from above or while wearing a backpack. Ethylenethiourea (ETU), a Type II B carcinogen, and antithyroid chemicals are produced when EBDCs are broken down.

Objective

The objective of conducting this research was to compare the occurrence of thyroid problems among EBDC-exposed mango plantation workers with ETU levels.

Method

90 employees between the ages of 20 and 52 who had been exposed to EBDCs directly or indirectly for at least two years each from four plantations that had been heavily reliant on dithiocarbamates over the previous ten years were chosen at random. These workers were most recently exposed 2 to 7 days prior to the start of the investigation. 40 control workers were chosen from an organic farm. These laborers lived at least 40 kilometers from the mango plantations and had no exposure to EBDCs. Weekly and daily applications of EBDCs were made using aerial and backpack spraying, respectively. In addition to or in instead of EBDCs, other fungicides such as chlorothalonil, propanol, and bioethanol were applied. Farmers were primarily exposed through skin contact and breathing. The Statistical Package for Social Sciences (SPSS) for Windows, version 10, was used to perform descriptive statistics, student t-tests, analyses of variance, Fisher's exact tests, Pearson's correlation analyses, and regression analyses.

Results

Despite being well within the normal range, the results showed that exposed workers had greater mean thyroid-stimulating hormone measurements than the control group. Compared to 2 in the control group, 10 of the exposed farmers showed abnormal thyroid ultrasonography results, which were primarily single nodules. Blood ETU levels among the directly exposed, indirectly exposed, and control groups were substantially different ($P<0.002$), although urine ETU levels were not ($P=0.11$; analysis of variance). Environmental ETU levels were below the threshold required for cleanup by the US EPA. A strong direct link between nodule size and blood ETU level in farmers with solitary thyroid nodules was observed.

Conclusion

According to this research, blood ETU is a more accurate biomarker of EBDC exposure than urinary ETU, hence medical surveillance programs for EBDC-exposed personnel should include blood ETU measurement to look for thyroid gland diseases.

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P794

Leukopenia A Benign Comorbitidy and Early Sign of Autoimmunity in Hashimoto's Thyroiditis

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Introduction

Leukopenia is a manifestation of autoimmune diseases such as systemic lupus erythematosus (SLE). Leukopenia may be an early sign of autoimmunity and may be a comorbidity in patients with autoimmune Hashimoto's thyroiditis.

Aim

The aim was to present a cohort of 12 patients with autoimmune Hashimoto's thyroiditis who presented with leukopenia.

Methods

A cohort of 12 patients, aged 19-72 y, female, with autoimmune Hashimoto's thyroiditis is described. Patients presented with leukopenia. Leukopenia was defined as a white blood cell count <4000 cells/mm^3.

Results

The white blood cell count remained <4000cells/mm^3 in a period of follow-up of 5-15 years. The white blood cell count varied in long-term follow-up. A female patient aged at diagnosis of Hashimoto's thyroiditis 42 y, developed breast cancer in her left and consequently her right breast at the age of 63 and had to receive chemotherapy. The white blood cell count deteriorated further during chemotherapy, but she was able to finish the therapeutic regimen. In long-term follow up her white blood cell count improved but remained <4000cells/mm^3.

Conclusions

Disorders of white blood cells may accompany autoimmunity. Neutropenia has been described in the context of autoimmune thyroid disease. Idiopathic neutropenia has been described as a benign disorder of granulopoiesis characterized by unexplained reduction in the absolute neutrophil count below

the lower limit of the normal for a prolonged period. It has been divided in primary autoimmune neutropenia characterized by autoantibodies against mature neutrophils and their bone marrow progenitors and chronic immunologic neutropenia characterized by suppression of granulopoiesis. Both disease entities usually display an uncomplicated clinical course with minimal symptoms. Leukopenia and lymphopenia have been described in the context of SLE. Leukopenia characterized by a benign clinical course may be an early sign of autoimmunity and may accompany autoimmune Hashimoto's thyroiditis. In conclusion, leukopenia may be a manifestation of Hashimoto's thyroiditis, especially in female patients and it is characterized by a benign clinical course.

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P795

Nivolumab-induced hypothyroidism: a case report

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Introduction
Immune checkpoint inhibitors are relatively new and promising treatments for a variety of solid tumors. Nivolumab is an anti-cancer monoclonal antibody that inhibits anti-programmed death-1 (PD1) and modulates T-cell response. It has been shown to significantly improve survival in many types of cancer, but clinical studies have also reported an increased risk of developing immune-related adverse events. In particular, immune-related adverse events may be related to the endocrine system. It has been reported that approximately 8% of patients treated with PD-1 inhibitors demonstrate hypothyroidism. We present a case of thyroid dysfunction caused by nivolumab.
Case
A 64-year-old male patient was treated with nivolumab for 10 months for tonsillar squamous cell carcinoma. He had no history of thyroid disease. Laboratory studies performed before the administration of nivolumab revealed normal thyroid function with normal levels of anti-thyroid peroxidase and anti-thyroglobulin antibodies. 9 months after starting treatment, the patient's thyroid stimulating hormone (TSH) levels suddenly increased to 57.70 mU/l (normal range 0.55–4.78 mU/l). Free T3 level was 1.65 pg/l (normal range 2.3 - 4.2 pg/l) and free T4 level was 0.24 ng/dl (normal range 0.89–1.76 ng/dl). We suspected nivolumab-induced hypothyroidism in the absence of other possible causes and started thyroid hormone replacement. The patient was followed as euthyroid with L-thyroxine 100 mg/day.
Conclusions
Immunotherapy has demonstrated significant clinical efficacy in many types of cancer. Immune checkpoint inhibitors aim to stimulate the immune system against cancer cells but should not be considered independent of some side effects. Thyroid dysfunction should be considered as a possible immune-related adverse event. Therefore, it is important to evaluate thyroid dysfunction at baseline and before the administration of each dose of nivolumab.

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P796

Assessement of Thyroid Function in An Obese Population

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Background
Obesity is an expanding pathology in the world and in Tunisia. We conducted this study to assess the thyroid function in a population of obese women and to investigate the relationship of thyroid status parameters with clinical and metabolic parameters.
Methods
This is a cross-sectional retrospective study about 50 obese women carried out at the obesity unit of department A of the National Institute of Nutrition in Tunis. We collected body mass index (BMI), waist circumference (W), serum free thyroxin (FT4) and thyroid stimulating hormon (TSH) levels, fasting glycemia (FG), baseline insulinemia, lipid profile, liver function, and body composition assessed by bioelectrical impedancemetry. We assessed insulin resistance and pancreatic activity by calculating the Homeostasic Model Assessment for Insulin Resistance (HOMA-IR) and the Homeostasic Model Assessment to quantify Beta-cell function (HOMA-B) respectively.
Results
The mean BMI and W were $41,2 \pm 9,3$ kg/m^2 and $120 \pm 17,7$ cm respectively. The mean body fat percentage (BF) was $43,4 \pm 7,1$%. The mean FT4 and TSH levels were $16,6 \pm 4,7$ pmol/l and $2,4 \pm 1$ IU/l, respectively. 2 patients had subclinical hypothyroidism. Glycoregulation abnormalities were noted in 54%. The mean insulinemia, HOMA-IR and HOMA-B were $23,4 \pm 14,8$ mIU/l, $6,5 \pm 5,1$ and $230,4 \pm 162,1$ respectively. 96% ($n=48$) had insulin resistance. TSH was not correlated with cardiometabolic risk parameters nor with BF. FT4 was correlated with age ($r=-0,3$, $P=0,017$), FG ($r=-0,29$, $P=0,019$), insulinemia ($r=-0,42$, $P=10^{-3}$), choesterol ($r=0,24$, $P=0,04$) and high density lipoprotein ($r=0,24$, $P=0,002$). It was not correlated with BF ($r=-0,14$, $P=0,32$).
Conclusion
In our population of obese women, FT4 seems to be more correlated than TSH with cardiometabolic risk parameters.

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P797

Congenital Hypothyroidism and Thyroid dyshormonogenesis: Clinical features and genetic findings

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Introduction
Thyroid dyshormonogenesis represents 15% of congenital hypothyroidism. It is a genetic disorder due to a trouble of Thyroid hormones synthesis. it implies many factors involved in this process mainly TPO Enzyme and NIS channel.
Methods
We conducted a prospective study including 17 patients with Congenital Hypothyroidism belonging to 4 consanguine multigenerational Tunisian families. The thyroid dyshormonogenesis was diagnosed based on clinical, biological and imaging exams. We assessed the mean age at diagnosis, clinical phenotype, hormonal and thyroid Autoantibodies, complications and the mean follow up duration. Meanwhile, we performed Audiometry exam to detect neurosensorial hearing defects.
Results
Our study included 17 patients with a sex ratio of 1,83 in favor of male sex. The mean age of diagnosis was 7 years old [1 month-30 years]. The mean TSH at Diagnosis was 54,92mUI/ml [5,2 -300]. The mean follow-up time was 10,11 years [4 to 24 years]. bilateral perceptive deafness was detected in only Three patients. Intellectual disability was severe in four cases and moderate in two. Two patients had fascial dysmorphia. they presented an enlarged saddle nose with a wide anterior fontanel associated with umbilical hernia. Thyroid autoantibodies were negative for all patients except two patients having Subclinical hypothyroidism. Biomolecular study of TG, NIS, PDS was negative for all patients, However segregation with S92STPO gene mutation was detected in all of them with evidence of a founder effect of the Tunisian population.
Conclusions
Congenital hypothyroidism may lead to severe complications which may be preventable if the disease is diagnosed and treated early, therefore the importance of screening for this disease is heightened. The discover of the founder TPO gene mutation will allow to perform genotype correlation that will guide diagnosis and screening.

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P798

Anaplastic transformation of papillary thyroid carcinoma in lung metastases:A case report

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Introduction
Anaplastic thyroid carcinoma is a subtype of thyroid carcinomas with an aggressive form. Anaplastic thyroid carcinomas are thought to develop as a result of differentiation of well-differentiated thyroid cancers. Anaplastic transformation of well-differentiated papillary thyroid carcinoma is very rare and most commonly occurs in thyroid gland and regional lymph nodes, whereas occurrence at distant metastatic site is extremely rare. Here we report the case of a patient with papillary thyroid carcinoma presenting with anaplastic transformation of metastases in the lung.
Case Presentation
An 80-year-old man presented with a 1 week history of dyspnea. His medical history included hypertension and papillary thyroid carcinoma, stage PT3N1bM0, for which he underwent total thyroidectomy, santral and lateral neck dissection and received radioactive iodine (RAI) therapy in 2008. 2 years ago, the patient was re-operated for recurrent disease and received second time RAİ therapy. Post-RAI scintigraphy was detected no involvement. Thyroglobulin and anti-thyroglobulin values were negative after RAI therapy. There was no metastasis in the thorax computed tomography (CT) imaging during this period. The patient; who did not come to follow up for 2 years, thorax CT was performed due to shortness of breath. Thorax CT scan showed metastatic nodules, the largest of nodules which 2.4 cm diameter in the lung and tissue densities compatible with recurrence including cystic necrotic areas extending to the pretracheal, right paratracheal, upper mediastinum in the thyroid gland lodge. Laboratory tests revealed TSH:0.94 mU/l (normal 0.27-4.2 mU/l) thyroglobulin:0.52 mg/l (normal 3.5-77 mg/l) anti-thyroglobulin antibody: 14 (normal 0-115 U/ml). Biopsy was performed from the mass in the thyroid lodge and the nodule in the lung. Histologic examination of thyroid mass and lung nodule revealed anaplastic thyroid carcinoma. Immunohistochemical staining for markers showed the presence of paired-box gen 8 (PAX-8) and absence of transcription factor 1 (TTF-1), and thyroglobulin (Tg). Tracheostomy was performed due to tracheal compression. Despite supportive treatment, his condition kept deteriorating and he was followed up in the intensive care unit. Subsequently, the patient died on the 15 th day of hospital admission.
Conclusions
We have described a case of anaplastic transformation of thyroid papillary carcinoma in the lung metastases, 14 years after initial presentation of papillary thyroid carcinoma. Anaplastic transformation of thyroid papillary carcinoma is a rare entity. It should be kept in mind that it can be seen with metastases years after diagnosis and considered in cases with aggressive clinical course.

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P799

Idiopathic Intracranial Hypertension and Grave's Disease

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Introduction
Idiopathic intracranial hypertension (IIH) is characterized by increased intracranial pressure without a detactable cause. Risk factors for the development of this syndrome are obesity and young female population. IIH due to hyperthyroidism is rare in the literature, mentioned in few individual case reports. The exact mechanism of how hyperthyroidism causes IIH is not known. We are reporting the case of a young women with Graves' disease presenting with symptoms of intracranial hypertension and blindness.
Case presentation
A 38 years old obese women with known Graves' disease, treated with monotherapy thiamazole, dose of 30 mg once daily during 3 years. Her condition unexpectedly deteriorated by associated moderate to severe active Graves' orbitopathy, headache, tinnitus, and blindness. Bilateral papillary pallor with blurred edges are found in fundus, the MRI and lumbar puncture showed increased intracranial pressure, but no underlying anatomical cause for the IIH was found. Patient was treated by High-dose systemic glucocorticoids and ventriculoperitoneal shunt. Unfortunately, no improvement of visual function were noticed.
Conclusion
This case report shows the importance of investigating for IIH in a hyperthyroid patient presenting headache associated with visual disturbances by performing a fundus, cerebral MRI angiogram, and CSF pressure measurement in order to preserve the visual function.

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P800

Assessment of educational needs of thyroid cancer patients during ablative iratherapy sessions

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Objective
To assess the educational needs of patients with differentiated thyroid carcinoma (DTC) undergoing ablative irradiation therapy (RAI131)
Patients and Methods
Cross-sectional study including 25 patients operated for TDC who integrated the therapeutic education program (TPE) on DTC at the Nuclear Medicine Center, Sfax, Tunisia. An assessment questionnaire was filled by the patients before the RAI session131
Results
Our group consisted of 19 women and 6 men, with an average age of 45.5 ± 15.2 years. This was the first treatment for 52% of the patients. RAI131 is a routine treatment for CDT for 64%. It is only necessary for severe/metastatic forms for 20% of respondents. RAI131 is used to 'destroy the cancer' (40%) and 'limit its spread' (44%). Contraception is recommended during treatment for 40% of patients. Defecation before the treatment was respected by 56%. Good knowledge of the low iodine diet (76%), its duration (56%) and its necessity for the success of the totalization (68%) was reported. Individual and community radiation protection rules were correctly recalled (95.8%). Isolation after RAI131 is essential according to 88% of patients for a duration > 5 days (73.7%). Questions about possible adverse effects of RAI131 were asked by 52% of participants.
Discussion
The success of isotopic totalisation for patients with CDT depends on good therapeutic and dietary preparation. ETP sessions with simulation of the procedure and reminder of the rules of radioprotection are essential.

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P801

Prevalence and factors associated with sleep disorders in patients with thyroid cancer

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Objective
To determine the prevalence and factors associated with sleep disorders in patients with differentiated thyroid cancer (DTC)
Patients and Methods
Analytical cross-sectional study of 39 patients followed for DTC at the Nuclear Medicine Center of Sfax, Tunisia. Sleep disorders were evaluated according to the 7 components of the Pittsburgh Sleep Quality Index (PSQI).
Results
The average age of the patients at the time of the survey was 44.5 ± 13.1 with a female predominance (92.3%). Pathological examination revealed a papillary variant in 89.7%. The response was excellent in 58.9% after a cumulative ablative irradiation of 265.9 ± 197 mCi. Patients had a mean disease-free survival of 4.6 ± 3.4 years. Hormone replacement therapy was chosen in all cases with a mean levothyroxine dose of 2.2 ± 0.4 µg/kg/day. The mean TSH at the time of the survey was 0.48 ± 0.89 mIU/l. These patients sleep on average 06 h an 45 minutes per day. The average sleep time was 41.5 ± 35.4 minutes. The average global PSQI score is high (7.7 ± 3.2 points). The prevalence of sleep disorders was estimated at 66.7%. The PSQI score was not significantly correlated with either the dose of levothyroxine prescribed or the degree of TSH suppression.
Discussion
The prevalence of sleep disturbances affects two out of three patients followed for DTC according to our results. This increased prevalence does not seem to be explained by subclinical hyperthyroidism for therapeutic purposes. Advice on lifestyle management during consultations is desirable to preserve the quality of life of this population.

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P802

Graves' disease associated with thymic hyperplasia: about a case

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Introduction
The association between Graves' disease and thymic hyperplasia was first described in 1912. Hundreds of cases have since been described. This rare association doesn't seem fortuitous. We report a case.
Observation
A 30-year-old patient with no particular personal history who consults following the onset of dyspnea with chest tightness. A CT scan of the chest revealed thymic hyperplasia. The preoperative assessment found an hyperthyroidism hence its orientation in endocrinology. A synthetic antithyroid drug treatment is started, and a CT reassessment after euthyroidism is proposed instead of surgery. A decrease in thymic hyperplasia is indeed observed after 3 months.
Discussion
Thymic hyperplasias are rare, except in adolescence. The persistence of a thymic remnant in adulthood raises fears of thymoma. The association of Graves' disease and thymic hyperplasia is to be known, it concerns 38% of patients, its evolution is benign and favorable under medical treatment with antithyroid drugs. What makes it possible to avoid unnecessary surgery, offers simple radiological monitoring.

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Late Breaking

P260

Effects of semaglutide, PYY3-36, and empagliflozin on the adrenal gland transcriptome in diet induced obese rats

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Background
An activation of the hypothalamic-pituitary-adrenal (HPA) axis is a common observation in obese individuals. GLP-1 agonists, such as semaglutide, and SGLT-2 inhibitors, such as empagliflozin, are well known to be beneficial in obesity, while other incretins, like peptide tyrosine tyrosine 3-36 (PYY 3-36), might be also useful for the treatment of obesity. However, the effect of these substances on the adrenal gland is largely unknown. We directly compared the effects of semaglutide alone and in combination with PYY as well as empagliflozin alone and in combination with semaglutide on adrenal gland transcriptomics.
Methods
High-fat diet (HFD)-induced obese male Wistar rats ($n=50$; mean bodyweight 260g) were randomized into the following treatment groups: semaglutide, semaglutide + PYY3-36, empagliflozin, semaglutide + empagliflozin, and saline. Animals had free access to high- and low-fat diet. After an observation period of 8 weeks, adrenal glands were taken out and evaluated using hypothesis-free RNA sequencing.
Results
Semaglutide and more pronounced semaglutide + PYY3-36 treatment led to weight loss, reduced overall food intake and (less pronounced) high-fat preference compared to saline treated controls. Empagliflozin had only mild effects on body weight. Interestingly, semaglutide + PYY3-36 treatment (compared to saline) led to a high amount of significantly upregulated genes ($n=320$) in the adrenal glands, which was much less pronounced in semaglutide and/or empagliflozin treated animals. Pathway analysis revealed a high number of activated pathways, most prominent among them: PI3K-Akt signaling, insulin signaling, renin-angiotensin system, neuroactive ligand-receptor interaction, adrenergic signalling.
Conclusions
Semaglutide + PYY3-36 combination therapy induces strong changes of adrenal gland transcriptome. Further analyses are necessary to identify exact mechanisms of GLP-1 and PYY based therapies on adrenal gland functionality, potentially leading to new treatment options for adrenal pathologies and for obesity related hypercortisolism.

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P261

Factored aldosterone can help distinguish mineralocorticoid resistance from aldosterone deficit hypoaldosteronism

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Introduction
Hypoaldosteronism can be induced by a deficit of aldosterone production (AldDef) or a mineralocorticoid resistance (MinRes). Experts have proposed to use hyperkalemia-based aldosterone values for this purpose. However, there is no a range of aldosterone values indicating one of this type of hypoaldosteronism. In 2008, Adam W. R.[1] hypothesized that the factored aldosterone (FAldo) could be useful differentiating hypoaldosteronism secondary to MinRes from AldDef. We aimed to determine the accuracy of aldosterone and FAldo values classifying hypoaldosteronism cases as AldDef or MinRes.
Methods
Retrospective study of adult cases of isolated hypoaldosteronism. Data from the aldosterone measurement day were analyzed. The presence of mineralocorticoid-resistance factors (ResF) was used to define hypoaldosteronism as MinRes. The absence of ResF defined hypoaldosteronism as AldDef. FAldo is obtained of the formula: blood aldosterone-ng/dl/(blood potassium-mmol/l– 4.2). FAldo value > 10 is suggestive of MinRes. The area under the curve (AUC) of the receiver operator characteristic (ROC) curve was used for determining the accuracy of aldosterone and Faldo values classifying hypoaldosteronism cases as MinRes or AldDef. Aldosterone values were analyzed both indistinctly from the presence of hyperkalemia and only in those with hyperkalemia. FAldo, since is already an aldosterone value corrected by kalemia, was analyzed indistinctly from the presence of hyperkalemia.
Results
88 hypoaldosteronism cases, age: 74 ± 13 years, 39 (46.4%) were female, 60/88 (68.2%) had MinRes. Mean FAldo values were different between those with and without MinRes (22.7 vs. 7.5 ng/dl/mmol/l, $P=0.007$). Mean Aldosterone values were also different between these groups (19.2 vs. 7.5 ng/dl, $P=0.032$). In the entire cohort, the AUC of FAldo for MinRes was 0.721 (95%CI: 0.61-0.83, $P=0.003$), while AUC of aldosterone values was 0.630 (95%CI: 0.51-0.75. $P=0.065$). During hyperkalemia, the AUCI of aldosterone values was 0.627 (95%CI: 0.48-0.78. $P=0.137$). The cut-off point of FAldo>10 had a sensitivity of 62%, a specificity of 81%, a predictive positive value of 90.2% and a predictive negative value of 43.6% to identify MinRes hypoaldosteronism.
Conclusions
A FAldo > 10 is suggestive of MinRes with a high accuracy. FAldo, indistinctly from the presence of hyperkalemia, seems to be more accurate than aldosterone values measured during hyperkalemia, to identify hypoaldosteronism induced by MinRes as defined by the presence of ResF. Clinicians could use this FAldo to identify etiopathogenic mechanisms in hypoaldosteronism patients.
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P262

Define cell-type-specific disease signatures regulating white adipose tissue of women with polycystic ovary syndrome

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White adipose tissue (WAT) is a dynamic and heterogeneous organ composed of different cell types involved in a wide array of biological processes. We know that women with polycystic ovary syndrome (PCOS) suffer from insulin resistance and type 2 diabetes which is associated with pathological white adipose tissue (WAT) function and expansion characterized by hypertrophic adipocytes, altered production and release of lipids and adipokines, and chronic low-grade tissue inflammation. We hypothesize that cell-type-specific WAT dysfunction contributes to insulin resistance and subsequent development of type 2 diabetes in women with PCOS and that treatment aimed at improving insulin sensitivity and reducing androgen excess has the potential to reverse these changes. Because our subcutaneous WAT are frozen and adipocytes are too large and fragile for traditional single-cell sequencing, in order to unravel the cellular complexity, we extracted single-nuclei (sn) from snap frozen WAT from controls ($n=4$) and from hyperandrogenic and insulin-resistant women with PCOS ($n=10$) at baseline and in PCOS after 16 weeks of metformin ($n=6$) or lifestyle management ($n=3$) for snRNA-sequencing using the 10x Genomics protocol. 200 million reads were sequenced from ~5,000 nuclei/sample. Pre-processing and quality control (QC) of the data was performed using CellRanger and Seurat 4.0 was used for downstream QC, filtering, integration, clustering and differential gene expression analyses.
Preliminary results
First we mapped all sequenced cells ($n=109,739$) from all subjects and identified four main canonical cell types based on the expression of known markers: 1) adipocytes ($n=17,896$); 2) adipose stem and progenitor cells (ASPCs) ($n=12,438$); 3) immune cells ($n=15,925$); and 4) vascular cells ($n=20,486$). Subclustering and differential gene expression within each subcluster, pathway- and functional analyses as well as defining the effect of metformin and lifestyle management are ongoing and will be presented.
Summary
These comprehensive analyses will significantly increase our understanding of the cellular complexity and heterogeneity in specific cell types underlying WAT dysfunction in PCOS, and define whether cell-type-specific molecular dysfunctions can be reversed by current first-line treatment.

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Are severe obese patients aging faster? The impact of severe obesity on different markers of biological age

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Obesity is defined as a state of chronic low-grade inflammation. It is associated with pro-inflammatory activity of visceral adipose tissue, regarded as a neuroendocrine organ that secretes cytotoxins and other pro-inflammatory factors, impairing metabolic pathways. The corollary of these changes is the risk of developing comorbidities. There are many similarities in the mechanisms of ageing and in obesity. The process of ageing leads to the accumulation of pro-inflammatory factors, activation of transcription factors responsible for promoting ageing (NFkB), impaired autophagy, impaired immune system function and increased senescence cells. Telomere length, levels of DNA damage and levels of inflammatory markers are considered hallmarks of ageing. Other markers of biological age are the level of cognitive function and metabolic age. The aim of this prospective cohort study was to assess the markers of premature ageing in people with extreme obesity: telomere length, DNA damage levels, IL-6 levels, cognitive function and metabolic age. All patients were recruited in 2nd Department of General Surgery in Jagiellonian University Medical College from July 2020 to May 2021. 133 patients were included and divided into two groups: SG - the extremely obese group (BMI $>=$ 40 kg/m2 or $>=$ 35 kg/m2 with comorbidity, $n=100$) and CG - the group of healthy volunteers (BMI between 18.5 and 24.9 kgm2, $n=33$). Blood samples were collected for serum and EDTA, DNA material was isolated for PCR telomere length assessment and enzymatic evaluation of 8-OHdG, the Wisocisin Card Sorting Test and the Colour Linkage Test were performed and body composition was analysed by bioimpedance. The SG group showed significantly shorter telomeres compared to CG (3957.4 vs 5191.53 bp) ($P=0.009$), higher IL-6 levels (4.57 vs 1.19) ($P<0.001$) and higher metabolic age (56.18 + -9.85 vs 37.12 + -12.8 years) ($P<0.001$). IL-6 levels were significantly influenced by percentage body fat ($P=0.043$). There were no statistically significant differences in cognitive function or levels of DNA damage in the extremely obese subjects compared to the control group. Obese patients are at a premature stage of ageing in terms of metabolic age and molecular age understood as telomere length. Elevated levels of chronic inflammation associated with body fat may be a factor in premature ageing.

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P264

A Novel Nonsense Variant in APOB Related to Familial Hypobetalipoproteinemia: A Case Report

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Purpose
Hereditary familial hypobetalipoproteinemia (FHBL) is an autosomal dominant disease group characterized by very low levels of lipoprotein including apolipoprotein-B (apo-B). FHBL patients are usually heterozygous and asymptomatic. Patients clinically diagnosed with homozygous FHBL are extremely rare. We aimed to present a 37-year-old adult patient with hepatosteatosis and neurological symptoms who had a homozygous missense c.737A>C (p.Gln246Pro) mutation in the APO-B gene, which has not been described in the literature before.
Case Report
The patient with primary hypothyroidism has the symptoms of ataxia, falling, myalgia, and steatorrhea; Total cholesterol: 21 mg/dl, Triglyceride: 19 mg/dl, HDL: 23 mg/dl, and LDL levels were found to be extremely low. Hepatomegaly was detected, muscle strength was complete, there was no motor deficit, but deep tendon reflexes were globally hypoactive. No pathological finding was detected in cranial MR and EMG. Grade-3 hepatosteatosis was seen in hepatobiliary ultrasonography, FIB-4 index was found to be 0.79. In the lipoprotein electrophoresis: Alpha: %93 (22-53), Beta: %4.4 (38-69) Chylomicron: 023) were detected. Stool evaluation of the patient with steatorrhea was positive for fat, pH:5, carbohydrate negative and stercobilin was normal. The percentage of acanthocytes was %50 and the eye examination was normal. Other laboratory findings; ALT: 48 U/l (<33), AST: 34 U/l (<32), INR: 1.06 (0.8- Prebeta: %1.7 (4-1.25), TSH: 1.8 mU/l (0,27-4.2), Vitamin-E: 1.2 mg/ml (5.5-18), Vitamin-A: 685 ng/ml (300-1000), Vitamin-D: 13 mg/l, APO-B: <20 mg/dl (60-117). MTTP gene mutation wasn't detected, c.737A>C (p.Gln246Pro) variant mutation was detected in the APO-B gene. In a short time with fat-soluble vitamin replacement, there were significant regression in neurological findings. In the first-degree relatives of the patient, a 14-year-old girl (Total cholesterol: 88 mg/dl, LDL: 37 mg/dl, Triglyceride: 47 mg/dl, HDL: 42 mg/dl, APO-B: 28 mg/dl, FIB-4 index: 0.17) and a 19-year-old boy (Total cholesterol: 89 mg/dl, LDL: 33 mg/dl, Triglyceride: 131 mg/dl, HDL: 30 mg/dl, APO-B: 44 mg/dl, FIB-4 index: 0.42) also has hypolipidemia and hepatosteatosis, APO-B heterozygous c.737A>C (p.Gln246Pro) variant mutataion was detected in their gene.
Conclusions
The case we present is the first description of the homozygous FHBL associated pathogenic mutation Apo-B c.737A>C (p.Gln246Pro) variant. Clinical suspicion associated with changes in the patient's lipid profile and subsequent genetic testing are very important in the diagnosis of FHBL. Identifying at-risk young relatives of an individual with FHBL through genetic testing will help identify those who would benefit from prompt initiation of treatment and preventive measures as early as possible.

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Investigating the role of deubiquitinases in adrenocortical carcinoma

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Adrenocortical carcinoma (ACC) is a rare endocrine malignancy presenting with an incidence of 1 per million per year and an overall 5-year survival rate under 35%. Currently, curative treatment is limited to full surgical resection, while the adrenolytic drug mitotane remains the only approved medical therapy option leaving a huge demand for innovative therapeutic strategies. Genetic alterations observed in ACC commonly lead to activation of Wnt/β-Catenin signaling most frequently caused by mutations in the CTNNB1 gene encoding for the nuclear effector β-Catenin. The key players of Wnt/β-Catenin signaling are known to be under tight control of the ubiquitin-proteasome-system. However, the role of deubiquitinases (DUBs) regarding β-Catenin regulation in ACC remains unknown. Analyzing publicly available data we preselected potentially relevant DUBs linked to patient survival in ACC and Wnt-Signaling. To confirm interesting targets, we performed quantitative PCR in six established ACC cell lines leading us to further investigation of USP10. We observed elevated protein abundance in primary tumor tissue compared to the normal adrenal gland as well as a high portion of USP10 in its active state across all ACC cell lines. Continuing the characterization of USP10 expression and localization, we performed immunohistochemical stainings on Tissue Micro Arrays (TMAs). Subsequential quantification of the TMAs incorporating a manually trained algorithm to distinguish tumor and surrounding tissue confirmed significantly higher USP10 expression in ACC as well as endocrine inactive adenoma compared to normal adrenal gland. Treatment with a Pan-DUB inhibitor, the proteasome inhibitor Bortezomib and a USP10-specific inhibitor led to a reduction of cell growth in ACC cell lines. In summary, we so far found strong indication for dysregulation of USP10 in adrenocortical tumors, therefore making it potential therapeutic target in ACC.

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Genetic profile of bone metabolism and immunity modulators in bone metastasis in castration-resistant prostate cancer

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Introduction
Prostate cancer is a neoplasm with high incidence and prevalence in the elderly population in western countries. Androgen deprivation therapy (ADT) has been used in locally advanced or metastatic disease, although most relapse, becoming hormone resistant, which is a poor prognostic event.
Objectives
The aim of this study was to evaluate the association of genetic polymorphisms NOS2, GPRC6A, VKORC1, ARGI and ARGII in prostate cancer, particularly to assess their predictive value for the development of hormone resistance in individuals under ADT therapy.
Methods
107 patients with PCa, aged 67-76 years, were included in this study. Most had PCa at an advanced stage, with 65.5% of patients having metastases at diagnosis. DNA was extracted from whole blood. NOS2, GPRC6A, VKORC1, ARGI and ARGII polymorphisms were detected using real-time PCR with Taqman probes and PCR-RFLP.
Results
Carriers of the NOS2 GG genotype were at higher risk for stage T3-T4. In the case of ARGI in the recessive model, that is, for the CC genotype, there is a 2.6 times greater risk for the existence of a PSA level greater than 20 ng/ml according to the univariate and multivariate analysis.
Conclusions
The ARGII GG genotype in the recessive model was related to early diagnosis of the disease. NOS2 and ARGI polymorphisms are associated with aggressive traits, while the ARGII variant affects earlier onset of prostate cancer.

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Risk of Impulse Control Disorders in Cabergoline-Treated Cushing's Disease: A Cross-sectional Study

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Aim
To determine the prevalence of impulse control disorder (ICD) in patients with Cushing's disease (CD) treated with cabergoline (CBG) compared to CBG-naive patients with CD.
Methods
We performed a cross-sectional study in patients with CD followed at 5 referral centers based in Istanbul. Eligible patients with CD were those with current CBG treatment for $\geq$ 3 months. Eligible controls were CBG-naive patients with CD that were matched for age and sex to CBG-treated patients. We administered Beck Depression Inventory, Beck Anxiety Inventory, and Symptom Checklist-90-Revised questionnaire to obtain a general measure of psychological distress. To evaluate impulsivity, both self-administered neuropsychological tests (Barratt Impulsiveness Scale, revised version of Minnesota Impulsive Disorders Interview, and Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale) and computerized behavioral tasks (Go/No-Go task, Iowa Gambling task, and Short Penn Continuous Performance Test) were used. All individuals underwent a detailed psychiatric assessment and the ultimate diagnosis of ICD(s), when present, was confirmed by an experienced psychiatrist. The measures of impulsivity and frequency of ICD(s) were compared between groups.
Results
A total of 34 CBG-treated patients with CD and 34 CBG-naive patients with CD were included. The mean age was 45.5 $\pm$ 11.6 in CBG-treated patients and 46.1 $\pm$ 13.5 in CBG-naive patients ($P=0.731$). In each group, 30 patients were female ($P=1.0$). The groups were similar in income, educational level, frequency of smokers, alcohol consumption, size of pituitary adenoma on last imaging study, frequency of hypogonadism and any psychiatric disorder. In CBG user group, the median duration of CBG use was 12 [IQR] 6-26.3 months. The median weekly CBG dose was 2 [IQR] 1-3.5 mg and cumulative dose was 61 [IQR] 30.6-146.4 mg. CBG-treated and CBG-naive patients showed no significant difference in measures of psychological distress and impulsivity. The most common psychiatric disorder in both groups was depression (35.3% vs. 29.2%, $P=0.796$). The frequency of any ICD was 8.8% ($n=3$) in CBG users and 5.9% ($n=2$) in non-users ($P=1.0$). In CBG-treated group, one patient was diagnosed with compulsive gambling (2.9%), one patient was diagnosed with compulsive shopping (2.9%), and another patient was diagnosed with both compulsive shopping and hobbysm (2.9%). In CBG-naive group, one patient with CD had compulsive gambling (2.9%) and one patient with CD had compulsive punding, eating, and hobbysm (2.9%).
Conclusions
Risk of ICDs may not be increased in CBG-treated patients with CD.

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Surgical outcomes in acromegaly: The influence of sex and menopause

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Introduction
Oestrogens and androgens modulate the effects of growth hormone (GH). Sex differences have been described in acromegaly, with conflicting results in different populations. Additionally, data on sex differences in tumour histopathology are scarce.
Aims
To analyse the influence of sex and menopause status in tumour characteristics and surgical outcomes in patients with acromegaly.
Materials and methods
Retrospective cohort study of patients with acromegaly submitted to transsphenoidal surgery, followed in a tertiary centre from 1988-2021. Postoperative biochemical remission was defined at $\geq$12 weeks by a normalization of insulin like growth factor-1 (IGF-1) and random GH $<$1ug/l or GH nadir $<$1ug/l after a 75-g oral glucose tolerance test. IGF-1 was presented as percent of upper limit of the normal value (%ULN). Differences in tumour size and invasiveness, hormone deficiencies, histopathology and surgical outcomes were compared between sex and pre/postmenopausal status at the time of diagnosis.
Results
We obtained a total of 65 patients: 44 women (12 postmenopausal), 21 men. Mean age at diagnosis in women was 48.1$\pm$12.1 vs 47.9$\pm$13.0 years in men (P=0.933), and mean IGF-1 was 296.3$\pm$126.9 vs 319.2$\pm$1221 %ULN (P=0.497). Pure somatotroph tumours accounted for 68.2% in women vs 71.4% in men, mixed somatotroph-lactotroph 25.0% vs 19.0%, plurihormonal PIT1+ 4.5% vs 9.5%, null cell 2.3% vs 0%. Somatotroph tumours were sparsely granulated in 83.3% of women and densely granulated in 75.0% of men (P=0.001). Postmenopausal women had less macroadenomas than premenopausal (47.1% vs 90.9%, P=0.004), lesser cavernous sinus invasion and suprasellar extension (16.6% vs 61.1%, P=0.016, and 30.8% vs 83.3%, P=0.003) and higher postoperative biochemical remission (52.6% vs 17.4%, P=0.016) and radiological remission at 1-year post-surgery (73.7% vs 27.3%, P=0.003), despite no differences in histopathology. Compared to women, men had a higher prevalence of hypogonadism at diagnosis (57.1% vs 22.7%, P=0.004) and lower rates of radiological remission (11.8% vs 47.6%, P=0.010). Tumour size was similar in men and premenopausal women (23.8 vs 26.0mm, P=0.546) and correlated inversely with age at diagnosis (r=-0.4, P=0.006). Men showed no significant differences regarding tumour invasiveness, postoperative biochemical remission or medical treatment response.
Conclusions
In our cohort men showed a higher prevalence of hypogonadism at diagnosis and lower radiological remission. Premenopausal women showed larger and more invasive tumours than postmenopausal, which may be due to younger age, but also to the oestrogen modulation of GH/IFG-1 axis. Differences in somatotroph tumour histopathology between sex may reflect a different impact of gonadal hormones in tumourigenesis.

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Salivary Alpha-Amylase Activity in Patients with Acromegaly: A Preliminary Report

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Objective
It has been argued that salivary alpha-amylase (sAA) is a potential indirect sympathoadrenal medullary (SAM) system activity marker. This study aimed to look at sAA to assess the sympathetic nervous system in acromegaly patients.
Subjects and Methods
A total of 31 individuals with acromegaly and 30 controls were enrolled in this prospective, single-center investigation. Saliva samples were taken from individuals with acromegaly and controls in the morning and at midnight. SAA activity were measured in patients with acromegaly and controls in the morning and at midnight.
Results
The morning sAA activity in the acromegaly group was 1.76 $\pm$ 0.38 U/ml, while the control group had 2.26 '13; 0.65 U/ml. Morning sAA activity were considerably lower in the acromegaly group ($P<0.001$) when compared to the control group. The midnight sAA activity in the acromegaly group was 1.79 $\pm$ 0.58 U/ml, and the midnight sAA activity in the control group was 2.19 $\pm$ 0.58 U/ml. When the two groups were compared, the midnight sAA activity of the acromegaly group was significantly lower (P=0.002). In addition, morning and midnight sAA activities were found to be similar between acromegaly groups with active and inactive diseases (respectively P=0.54, P=0.63).
Conclusions
This study showed that sAA activity, which is used as an indicator of sympathetic nervous system activity, was decreased in the acromegaly group compared to the control group. Additionally, morning and midnight sAA activity between acromegaly groups with active and inactive disease were similar. Further studies with larger sample sizes are needed to show the link between sympathetic nervous system activity and sAA activity in acromegaly.

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Overlapping syndromes - Turner and X-linked Kabuki associated with Short Stature

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Introduction
Kabuki syndrome (KS) is a rare congenital, multisystemic disorder caused by pathogenic variants of KMT2D or KDM6A genes, causing autosomal dominant KS type 1 (more than 80%) and X-linked KS type 2 respectively. The phenotype spectrum is highly variable, consisting of a mixture of any of the five cardinal features (facial dysmorphic features, skeletal defects, dermatoglyphic abnormalities, various degrees of intellectual and growth retardation) with structural disorders comprising ophtalmologic, auricular, dental, cardiac, gastro-intestinal, genitourinary disorders and other conditions such as seizures, autoimmune or endocrine-related disorders (growth hormone deficiency (GHD), hyperinsulinemia, delayed sexual development, early thelarche or diabetes insipidus).
Case report
Our 4-year-old female patient was born prematurely via caesarian section at 32 gestational weeks, with a birth weight of 2300g. She had a history of infantile hypotonia, developmental delay, astigmatism, right renal hypoplasia and medullary nephrocalcinosis treated with Hydrochlorothiazide. At the first assessment in the Endocrinology clinic, she presented prominent, low-set ears, long palpebral fissures, flattened nose, enlarged thorax base, short stature at -3.04 SD according to Romanian synthetic growth charts, at -2.08 SD compared to the target height, healthy weight at 11th percentile and a perfectly normal neuropsychomotor development. The genetic test was positive for a heterozygous complete deletion of the coding regions of KDM6A gene, and the karyotype disclosed a Turner mosaicism 46,X,i(X)(q10)/45,X/46,XX[17]/[14][1]. IGF-1 level was in the normal range, the GH secretion was not stimulated consecutive to glucagon administration.
Discussions
The occurrence of both Kabuki and Turner syndrome has been cited in several case reports, and may express overlapping features, such as short stature, hyperinsulinism or congenital heart diseases. The clinical characteristics of X-linked KS type 2 have been less studied than the 1st type. The females were observed to be less prone to severe phenotypes than male-affected individuals. Short stature is a common feature in patients with KS, not necessarily related to GHD; however, the genotype-phenotype correlations suggest a direct relationship with KMT2D mutations, while short stature is less frequent in the KDM6A group. Turner karyotype serves as an indication for rh-GH therapy, which may significantly improve the prognosis of our patient.

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Monitoring serum estradiol levels in clinical practice: a retrospective study in transgender AMAB subjects

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The Standards of Care version 8 (SOC 8) for transgender and gender diverse people suggest maintaining estradiol (E2) levels between 100-200 pg/ml in Assigned Male at Birth (AMAB) subjects who desire a complete feminization during gender affirmation hormone therapy (GAHT). However, data about estrogen dose therapy and corresponding serum concentrations are scarce, especially regarding gel formulations. Our aim was to retrospectively compare E2 serum levels in AMAB patients undergoing GAHT according to the different formulations and dose used. All subjects were treated with either oral estradiol valerate (OE) or transdermal estradiol gel 0.1% (TDE), according to SOC 8. Three different groups were identified according to the dose of E2 administered: low dose (LD), medium dose (MD), and high dose (HD) [$\leq$ 2, 3-5, $>$6 mg/day for OE and $\leq$ 1, 1.5-2.5, $\geq$3 mg/day for TDE, respectively]. 135 serum E2 measurements were collected among 79 subjects undergoing GAHT. 34.1% of samplings (46/135) were collected in subjects on OE, while 65.9% (88/135) were collected in subjects on TDE. OE was administered in 23.9% of cases at LD, 60.9% at MD and 15.2% at HD, while TDE was administered in 14.6% of cases at LD, 44.9% at MD and 40.4% at HD. Overall, E2 levels showed a wide spreading: 165.8$\pm$264.0 pg/ml (16.7 - 2613.6). Serum levels in patients taking TDE (214.7$\pm$311.6 pg/ml) were significantly higher ($P<0.001$) than those in OE (71.1$\pm$61.6 pg/ml). Stratifying by dose, significance was maintained in MD and HD groups ($P<0.001$), with a trend toward significance for the LD groups (P 0.055). Overall, only 23.7% of the measurements were within the desired range: in subjects taking EO were within, below and above range in 15.2%, 80.4% and 4.3% of cases, while in subjects taking TDE were within, below and above range in 28.1%, 38.2% and 33.7% of cases, respectively ($P<0.001$). No significant differences were found according to the dosage used for each formulation. In conclusion, despite the dosage of GAHT was consistent with the SOC 8 recommendations, E2 levels were often out of target, with patients taking OE showing lower values than those taking TDE. This result could suggest both a greater efficacy of TDE compared with EO at doses typically used and an underestimation of the measured concentration in EO (as found in recent studies), and it should be considered for the interpretation of estradiol values measured in clinical practice.

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Predictors of Quality of Life in Treated Hypothyroidism

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Background

Despite receiving biochemically adequate levothyroxine replacement, many patients with primary hypothyroidism suffer from persistent symptoms and a reduced quality of life (QoL). The underlying causes of this phenomenon are not fully understood, but psychological factors, autoimmune inflammation, and variations in thyroxine conversion have all been suggested as potential contributors. At this time, however, there is no consensus on the root cause.

Methods

In this cross-sectional study we aimed to explore the potential impact of various demographic, anamnestic, psychometric, and laboratory predictors on disease-specific quality of life, as measured by the Thyroid-Dependent Quality of Life questionnaire. To minimize confounding factors, we applied stringent inclusion criteria including a disease duration of at least two years, a stable thyroxine dose and normal TSH level for at least six months, and no significant medical or psychological comorbidities. The assessed psychometric covariates were somatization (Somatosensory Amplification Scale), depression (Patient Health Questionnaire-9), and symptom number (Underactive Thyroid Symptom Rating Questionnaire). Determinants of QoL were assessed using uni- and multivariate linear modeling with robust corrections, as well as mediation analysis.

Results

Our final study sample consisted of 157 patients, of whom 70.7% had Hashimoto's thyroiditis and 29.3% had hypothyroidism of iatrogenic origin (eg. cancer, thyroidectomy, or post-radioiodine treatment). The mean age of participants was 49.5 $\pm$ 14.5 years, average disease duration 11.2 $\pm$ 8.2 years, thyroxine dose 1.2 $\pm$ 0.4 mg/kg body weight, and a TSH level 1.8 $\pm$ 0.9 mIU/l. We found no significant association between QoL and thyroid-specific laboratory parameters, including TSH, FT3, FT4, rT3, anti-TPO, and SHBG. Using a multivariate model we identified somatization (B=-0.59, $P=0.005$), BMI (B=-0.08, $P=0.015$), and symptom number (B=-0.11, $P=0.043$) as the primary determinants of quality of life ($r^2 = 0.34$). Mediation analysis also revealed a significant indirect effect of depression on QoL, mediated primarily by somatization and BMI. In this later model 49% of the variation in symptom number was related to depression and somatization. After adjusting for psychometric factors, etiology had no effect in either analysis.

Conclusions

Our study suggests that psychological factors play a paramount role in determining quality of life of hypothyroid individuals receiving adequate levothyroxine replacement. Our findings do not support the notion that autoimmune inflammation or tissue-level hypothyroidism has a significant influence on QoL.

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Management of Thyroid Nodules- a single centre experience/ a district Hospital Experience

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Background

A thyroid nodule is a discrete lesion within the thyroid gland, which can serve as a prelude to a spectrum of conditions ranging from a benign incidental growth to a full-blown invasive carcinoma. Thyroid nodules are very common in adult population. About 15% of the UK population have clinically detectable goitres or thyroid nodules, and the lifetime risk of developing a thyroid nodule is around 5 to 10%. In addition, there is increasing risk of thyroid cancers in the UK, numbers having more than doubled since the 1970s, and estimated to climb to 74% between 2014 and 2035. 1 Therefore, it is crucial to follow a defined protocol for investigation and risk stratification of such nodules, while ensuring judicious use of available resources.

Aim and Method

A retrospective study was undertaken in the East London District Hospital with the aim to assess the management of thyroid nodules in keeping with the guidelines published by British Thyroid Association Guidelines for Management of Thyroid Nodules (2014). We enrolled random patients who had been diagnosed with thyroid nodules on ultrasound imaging of the neck. We collected data from 50 patients, such as U score in their ultrasound reports, how they were followed up and the outcome of follow up. These data were analysed, by tracking their progress to date after being diagnosed with thyroid nodule.

Standards

We compared against the BTA thyroid nodule management guidelines (2014) which recommend that: (1) all thyroid ultrasounds should report U-score on thyroid nodules (2) U1-U2 nodules does not require fine needle aspiration cytology (FNAC) (3) U3-U5 requires further follow up with FNAC.

Result

According to this study, more than three-quarters of the cases appropriately met the standards defined in the BTA guidelines. Nearly ten percent of thyroid nodules were found to be thyroid cancers upon follow up. Less than 2% of ultrasound reports did not include a U score for thyroid nodule identified.

Conclusions

It was deduced that the follow up management plan for thyroid nodule cases was satisfactory within 2022. However, there are still some areas to emphasize for further perfection. It would be beneficial to introduce educational interventions including departmental teaching in order to ensure compliance to latest guidelines, for suitable follow up according to clinical indication, with the ultimate goal of positive impact on patient care.

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St. John's wort as an example of the naturalistic fallacy: natural things are not necessarily good things

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Introduction/Aim

New oral anticoagulant drugs such as the factor Xa inhibitor rivaroxaban are often preferred to the classic coumarins because they do not need frequent blood-test monitoring and have fever interactions with other drugs and foodstuffs. They are not, however, interaction free. Rivaroxaban is metabolized by oxidative degradation catalyzed by CYP3A4/5 and CYP2J2; it is also a substrate of the P-gp and ABCG2 efflux transporter proteins. CYP3A4 activity enhancers such as phenytoin, carbamazepine, phenobarbital, rifampin, and the herbal antidepressant St. John's wort may decrease the efficacy of factor Xa inhibitors and increase the risk of thrombosis and embolism. We hereby report the case of a patient who presented recurrence of deep vein thrombosis (DVT) complicated with severe pulmonary embolism in spite of treatment with rivaroxaban, associated with the intake of Saint John's wort.

Methods

Review of the patient's record and the relevant literature.

Results

A 54 year old, non-smoker female patient with type 2 diabetes, obesity, sedentarism, hypertension and dyslipidaemia had recurrent episodes of DVT in both calves, and had been diagnosed of factor V Leiden deficiency. Treatment with acenocoumarol was prescribed, but her INR values were erratic; moreover she had several episodes of minor bleeding, and her treatment was switched to rivaroxaban 2.5 mg/12 h + AAS 100 mg/day. The patient remained asymptomatic for two years. Afterwards, the patient was admitted to the Emergency Room with sudden-onset dyspnea, tachypnea, tachycardia, hypotension, diffuse pleuritic chest pain, cyanosis and sincope. She had noticed tenderness, redness and swelling in her right calf during the previous week. Chest auscultation showed disseminated sibilant rales, and her pulse oximetry was 91%. DVT and pulmonary embolism were suspected and confirmed by calf ultrasonography and thoracic CT scan. Intravenous heparin therapy was begun along with support measures, and the patient was discharged on subcutaneous low molecular weight heparin after five days. When questioned again before discharge, she revealed self-medication with a non-prescription St. John's wort (Hypericum perforatum) preparation over the previous 3 weeks, motivated by depressive symptoms related to family issues.

Conclusions

Depression is a frequent comorbidity of DVT and the use of non-prescription herbal antidepressants such as Saint John's wort is often not reported by the patients. Saint John's wort may treble the activity of CYP3A4 and impair the effect of factor Xa inhibitors such as rivaroxaban with potentially serious consequences. The awareness of this interaction among the prescribing physicians is low and should be enhanced.

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Functional and morphologic aspects of fetal adrenal before/after freezing/thawing and 14 days in organotypic culture

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Introduction

The human fetal adrenals (HFA) produce high levels of steroids. The gland is distinguishable from the 7th gestational week and can be separated in two zones: the fetal zone in the center which correspond of 80 % of the gland and the definitive zone in the periphery. At this time of the development, neural crest cells are reaching the adrenal primordium, producing catecholamines. A third zone, the transitional zone appears later in the early 2nd trimester. The objective of our study is to evaluate the functionality of adrenals after freezing, thawing and cultured in 'hanging drops' for 14 days.

Tissues and Methods

Adrenal tissues from surgical elective abortions at 9-13 weeks of gestation was cut in several fragments of 1mm^3 and cultured in 'hanging drops' either straight after dissection or after vitrification or slow freezing and thawing in a drop of 40 µl of media containing ACTH 1ng/ml or not. Twelve steroids were measured by LC-MS/MS in medium recovered all along the culture and the expression of CYP17 was explored by immuno-histo-chemistry (IHC) after 2 weeks of 3D culture.

Results

Steroidogenesis is persistent after 2 weeks in organotypic culture and ACTH stimulate cortisol, cortisone and corticosterone secretion. After vitrification or slow freezing procedure, steroid secretion was similar. Analysis is in progress to compare the IHC results between the first and the second week of culture and between the tissues that have been frozen and those that have not.

Conclusion

We showed that 1er trimester fetal adrenals can produce steroids after vitrification or slow freezing and 2 weeks in organotypic culture. Adrenals, as gonads, derivate from the mesoderm. Indeed, the optimization of these techniques could help us to enhance the freezing/thawing protocols of immature testicular tissue in the context of fertility preservation of prepubescent youth.

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Occurrence of thyroid autoimmunity, metabolic disorders and malignancy in patients with primary, non-syndromic hyperparathyroidism

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Background/aim

Primary hyperparathyroidism (pHPT) is a relatively common endocrine disorder, which is often asymptomatic and thus diagnosed during routine biochemical testing. Emerging scientific data supports the theory that non-syndromic pHPT patients may be at increased risk for thyroid autoimmunity, metabolic disorders and malignancy.

Materials and methods

A cohort of 227 pHPT (61 male and 166 female) and 244 non-pHPT (75 male and 169 female) patients from our endocrinology outpatient clinics was included in the retrospective study. Demographic, clinical and laboratory data of these patients were evaluated retrospectively.

Results

Mean age and body mass index of pHPT and non-pHPT patients were comparable (60.3 vs 58.1 years, $P=0.21$ and 28 vs 27.1 kg/m^2, $P=0.58$). pHPT affected more often female patients (166/227-73%) Autoimmune thyroid disease (AITD) was more prevalent among pHPT patients (78/227 [34.4%] vs 26/244 [10.6%], $P=0.01$). pHPT patients had more often diabetes mellitus (DM) (46/227 [20.3%] vs 23/244 [9.4%], $P=0.026$). On the contrary, obesity ($P=0.24$) and impaired fasting glucose (IFG) ($P=0.36$) were equally observed among the groups. The overall occurrence of cancer was increased among the pHPT patients (59/227 [26%] vs 38/244 [15.5%], $P<0.01$). The most commonly observed malignancy among all patients was differentiated thyroid cancer, which was more prevalent among the pHPT patients (19/227 [8.4%] vs 12/244 [4.9%], $P=0.014$). Regarding other malignancies, pHPT patients exhibited higher malignancy rates (40/227 [17.6%] vs 26/244 [10.6%], $P<0.01$). Among the pHPT patients, breast cancer was more frequent (12/227 patients), followed by lung and uterus cancer (7/227 and 4/227 patients respectively). Among non-pHPT patients, breast, lung and intestinal cancer were more prevalent (9/244, 5/244 and 3/244 patients, respectively). Finally, among pHPT patients, female patients suffered more often from AITD (65/166 [39.1%] vs 13/61 [21.3%], $P<0.01$) and DM (36/166 [21.7%] vs 10/61 [16.4%], $P=0.02$). Additionally, women were more obese (84/166 [50.6%] vs 11/61 [18%], $P=0.01$) and had more often IFG (8/166

[4.8%] vs 2/61 [3.3%]. $P=0.04$) than men. Interestingly, the prevalence of cancer was equal among male and female pHPT patients (16/61 [26.2%] vs 43/166 [25.8%], $P=0.15$).
Conclusions
Non-syndromic pHPT may be associated with increased risk for concomitant thyroid autoimmunity, metabolic disorders and malignancies. Thus, clinicians should be alert and routinely evaluate these patients for the previous mentioned pathological entities.

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Role of insulin therapy in weight gain: lessons from islet transplantation in type1 diabetes

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Background
Weight gain in type 1 diabetes (T1D) patients has become a clinical problem due to less strict diets and more stringent glycemic targets. Thus, the number of overweight T1D in the USA increased from 3.4% in 1988 to 22.7% in 2007. Hyperinsulinism is involved in the genesis of obesity but in T1D, the impact of insulin therapy in weight gain is not established. Islet transplantation, now reimbursed in France, makes it possible to interrupt insulin. The aim of this work was to study weight evolution in an islet-transplanted population after obtention of insulin-independence and to determine the weight predictive factors.
Methods
monocentric retrospective study comparing the evolution of anthropometric and metabolic parameters before and 1, 3, 5 and 10 years after islet transplantation alone performed between 2003 and 2017, in 41 patients.
Results
The population (21 women, 20 men), aged (median (IQR)) 48 (42-55) years, had a weight of 71.4 (66-78) kg, a BMI of 24.7 (22.9-26) kg/m^2, a body fat percentage (DEXA) of 26.3 (20.0-31.5) %, and a daily insulin requirement of 41.3 (30.5-47.0) IU/day. The median weight loss at 1, 3, 5 and 10 years was 6.6 ($P=0.003$), 4.9 ($P=0.007$), 5.0 ($P=0.043$), and 5.4 kg ($P=0.418$) respectively, and correlated with the decrease in insulin doses ($r^2=0.295$; $P=0.0005$) at 5 years. In the 18/41 patients with a pre-transplantation BMI >25 kg/m^2, 10-year weight loss was permanent, unlike in the 23/41 patients with pre-transplantation normal BMI. The glycemic balance was identical between the 2 groups.
Conclusions
A weight loss is observed with islet transplantation, more marked in initially overweight subjects and correlated with the insulin dose decrease. These results suggest a role of exogenous insulin therapy in the weight gain of T1D patients, that is likely to limit their access to islet transplant, since a BMI below 28-30 is usually required is a favorable factor to gain insulin-independence after islet transplantatin. The latter, however, could be modulated by the level of insulin-sensitivity.

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Abstract withdrawn

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How did COVID-19 pandemic affect the glycemic regulation of patients with type 1 diabetes mellitus and continuous insulin infusion systems? Experience of a single diabetes center

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Background and Aims
The COVID-19 pandemic severely affected the glycemic regulation of adult patients with type 1 diabetes (T1D). The aim of this study was to evaluate the impact of this pandemic on glycemic control in T1D patients with continuous subcutaneous insulin infusion (CSII) systems.
Methods
A cohort of adult T1D patients with CSII was retrospectively evaluated. Data regarding number visits to our diabetes clinics, total daily insulin dose (TDID), blood and estimated HbA1c (b- and eHbA1c), time in range (TIR) (70–180 mg/dl), time below range (TBR) (<70 mg/dl) time above range (TAR)(>180 mg/dl) and coefficient of variation (%CV) in the pre- (March 2018- March 2020) and the pandemic (April 2020- April 2022) were collected.
Results
66 patients were studied (32 females) with mean age 44±12.1 years, mean body mass index [BMI] of 25.1±4 kg/m2 and mean total daily insulin dose (TDID) was 37±4.3 IU. Patients had a moderate glycemic control (mean bHbA1c 7.3±0.9%) while the mean estimated HbA1c (7.15±0.9%) (glucose management indicator or GMI) was slightly lower. Mean sensor use of patients was satisfactory (92.5%) while %CV (34.1±5.5%), which reflects intraday glycemic variability (GV), was marginally higher than normal. The average number of visits in the prepandemic period was 8, with a relatively strong negative correlation between this number of visits and HbA1c ($r=-0.65$) During the pandemic period, both BMI (25.1±4 vs 24.4±3.3 kg/m2, $P=0.11$) and TDID (37±4.3 vs 36.1±3.6 IU, $P=0.33$) remained stable. On the contrary, TIR increased significantly (65.8±8.6 vs 70.2±16.8%; $P=0.026$) while TBR (5.8±4 vs 4.9±3.8%; $P=0.007$) and TAR (28.4±5.4 vs 24.9±3.3%; $P=0.03$) diminished substantially. Furthermore, mean bHbA1c (7.3±0.9 vs 7.15±0.7%; $P=0.01$), eHbA1c (7.15±0.9 vs 6.94±0.65%; $P=0.005$) and %CV (34.1±5.5 vs 31.7±4.1%; $P<0.001$) decreased considerably during the pandemic. Additionally, the average number of visits was reduced to 4 per person in the postpandemic period and this number was moderately and negatively correlated with glycemic control ($r=-0.45$).
Conclusions
Glycemic regulation of adult patients with T1D and CSII improved significantly during the pandemic, despite reduced visits to the diabetes outpatient clinics.

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Somatic RET M918T variant can modify the natural history of MEN2 related medullary thyroid carcinoma: a case report and literature review

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Background
Multiple endocrine neoplasia type 2 associated medullary thyroid carcinoma (MTC) is driven by a strong genotype-phenotype correlation, the risk of aggressiveness being defined by the germline *RET* pathogenic variant (American Thyroid Association (ATA) guidelines). Based on this classification, the germline c.2370G>C, p.Leu790Phe (L790F) *RET* variant is considered to be of moderate risk of aggressive MTC, while the germline c.2753T>C, p.Met918Thr (M918T) *RET* variant presents the highest risk. In non-hereditary MTC, the somatic *RET* M918T mutation is also the main driver mutation of tumorigenesis and correlates with a worse outcome.
Patient findings
A 35-year-old woman presented with highly suspicious right thyroid nodule. Preoperative calcitonin and Carcino-embryonic antigen (CEA) were 2300 pg/ml and 21 ng/ml, respectively. Total thyroidectomy with neck dissection revealed a pT3N1b MTC. Genetic screening identified a moderate risk ATA germline *RET*-

mutation (*RET* L790F). As the patient rapidly developed lung and bone metastases, a genetic screening was performed on the MTC: a somatic *RET*-mutation (*RET* M918T) was identified explaining the rapidly aggressive phenotype presented by the patient. At last follow-up, six years after surgery, calcitonin and CEA were 6566 pg/ml and 84.2 pg/ml, respectively. Imaging investigations showed a persistent metastatic disease with cervical-mediastinal nodes, lung and bones metastasis. The patient showed no other manifestation belonging to the MEN2 spectrum. Her family member were screened for the germline variant and all carriers had normal calcitonin and neck ultrasound.

Discussion

We report the case of a double germline and somatic *RET* pathogenic variants, leading to a more aggressive profile than what the germline genetic screening was suggesting. Most of the studies reporting the natural history of MTC associated with *RET* L790F variant are in favor of an indolent disease. A large French multicentric study involving 77 patients with *RET* L790F germline mutation reported no distant metastases. Lymph node invasion was reported in 10/55 (18.2%) operated patients, with an early age of 32 years. After a 89-month follow-up, most of both index and screened patients were cured. On the other hand, several studies reported that patients with somatic *RET*-mutated MTC (mainly *RET* M918T) have a more advanced stage at diagnosis and experienced a worse outcome. The identification of additional somatic RET variant in addition to preexisting mutation in patients with hereditary MTC have been rarely reported and may promote tumorigenesis *in vivo*. Thus, this situation emphasizes the need to think differently when genotype and phenotype don't match in MEN2 related MTC.

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Systemic inflammation in paragangliomas and pheochromocytomas

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Background

Paragangliomas (PGLs) and pheochromocytomas (PCCs) arise from chromaffin cells. We evaluated the inflammatory markers. The pan-immune-inflammation value (PIV) has recently been used as a new marker. Therefore, we evaluated the PIV association in patients with PGLs/PCCs.

Methods

In the study, the data of 82 patients with PGLs/PCCs who applied between 2005 and 2020 were collected retrospectively from the records. NLR (neutrophil/lymphocyte ratio), PIV (pan-immune-inflammation value), PLR (platelet/lymphocyte ratio) values were calculated with the parameters measured from peripheral blood. These patients were compared with 47 healthy controls.

Results

PIV measurement was found to be higher than that of the control group ($P=0.028$; $P<0.05$). NLR measurement was also statistically significantly different ($P=0.001$; $P<0.01$). According to the ROC analysis, the most appropriate cut-off value for PIV to identify groups is ≥ 296.87.

Conclusion

As far as is known, our study is the first study with PIV in this patient group. This value was found to be significantly higher in the patient group. More studies are needed before it can be used as a marker.

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In silico approaches advocates the sensitivity of adrenal gland against EDCs shown in male Wistar rats

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Adrenal gland is a less focused endocrine organ for the endocrine disrupting effect of endocrine disrupting chemicals (EDCs). The effects of two extensively used phthalate esters viz. di-ethyl hexyl phthalate (DEHP) and di-butyl phthalate (DBP) on adrenal gland were observed in Wistar rats in the present study to check the susceptibility of adrenal gland against the exposure of these extensively used plasticizers which are well known EDCs. Wistar rats were divided into seven groups ($n=5$) and received the treatment for fourteen days. Group I was control and received only corn oil which is used as vehicle. Group II, III and IV received daily dose of DEHP of 250 mg/kg-BW, 750 mg/kg-BW and 1500 mg/kg-BW respectively while group V, VI and VII received daily dose of DBP of 100 mg/kg-BW, 500 mg/kg-BW and 1000 mg/kg-BW respectively. The comparative microscopic study of histological slides of endocrine glands i.e. pituitary, pineal, thyroid, parathyroid, adrenal gland and testes revealed the susceptibility of adrenal gland towards the DEHP and DBP. Molecular docking and protein-protein interaction (PPI) studies of DEHP and DBP have been employed using Maestro Schrodinger 9.4 software and STRING database showing the potential of DEHP and DBP to compare the molecular targets of above mentioned endocrine glands. Molecular docking and PPI studies advocates the sensitivity of adrenal gland as second most sensitive endocrine gland after testes by showing promising interaction with biochemical indices of adrenal gland. Therefore, further molecular studies are advised to divulge the molecular targets of EDCs and molecular mechanism underlying through them.

Keywords
DEHP, DBP, phthalate esters, molecular docking, protein-protein interaction
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Characterization of RNA expression and clinical outcomes in patients with aggresive pituitary tumors treated with temozolomide

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Methods

Descriptive retrospective study of the clinical outcomes and RNA expression in aggressive pituitary tumors treated with temozolomide. RNA expression was studied in tumor samples normalized to housekeeping genes including GH, POMC, PRL, αsub, FSH, LH, TSH, sst1, sst2, sst3, sst5, sst5b, sst5c, DR1, DR2T, DR2L, DR4, DR5, Ghrelin, In1-Ghrelin, GOAT, GHRR1b, AVPR1b, GHRH-R, GnRH-R, Ki-67, PTTG1, CRHR1.

Results

Ten patients were treated. 30% (3) prolactinoma, 30% (3) Cushing's disease, 40% (4) NFPT. 30% (3) pituitary carcinomas. Median presentation size was 32 [30-37] mm, historical maximum size 33 [30-37] mm. At presentation, 80% (8) had invasion of the cavernous sinus, and 90% had supra-chiasmatic invasion. 50% (5) ACTH, 10% (1) null cell, 10% (1) GH, 20% (2) PRL and isolated GH, and 10% (1) PRL. Ki-67 greater than 3% in 80% (8), Ki-67>10% in 40% (4). The median number of previous interventions was 2 [2-3]. 60% (6) had received previous radiation therapy, while the rest received it concurrently, with 40% (4) receiving it via the STUPP protocol. The number of cycles received was 17 [6-27]. The RNA expression of Ki67 and PTTG1 was found to be elevated in pituitary carcinomas. The expression of Ghrelin was found to be greatly increased in carcinomas and aggressive tumors, with patients who died having higher levels than survivors. The median maximum size prior to TMZ was 23 [19-30] mm, and at 6 months of treatment, the median maximum size was 17.5 [14-23] mm. A partial response was observed according to RECIST in 40% (4) of cases at 6 months, with one patient achieving partial response criteria after more than 6 months. The median time to maximum response was 0.48 [0.38-1.29] years. Progression was observed in 40% (4) of cases, with a median time to progression from the start of TMZ of 1.61 [1.11-2.32] years. Currently, 50% (5) of patients are not on TMZ treatment, 30% (3) due to progression and complementary treatments, and 10% (1) due to patient relocation. No serious adverse effects were observed, but asthenia was observed in 40% (4) of patients.

Conclusions

The treatment with temozolomide is safe in aggressive pituitary tumors and allows for achieving an initial response and medium-term stability. The

expression of certain RNAs (Ghrelin, PTTG1) may allow for estimating long-term aggressiveness risk and mortality.

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Synovial sarcoma in a patient with long-standing acromegalia: Causal vs. coincidental

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Introduction

Acromegaly is associated with many different types of benign and malign neoplasm, putatively because of the chronic elevation of IGF-1. Colorectal, thyroid and breast neoplasms are well-established associations; there are many other possible ones, such as prostatic and uterine neoplasms, meningioma, leukemia, lymphoma, renal, pulmonary, esophageal and gastric tumors. Also in the context of MEN-1, parathyroid and pancreatic neoplasms are associated with acromegaly. Synovial sarcoma is an infrequent and very aggressive malignant tumor characterized by a specific chromosomal translocation which fuses the SYT gene from chromosome 18 to a homologous gene (SSX1 or SSX2) at Xp11, resulting in the fusion proteins SYT-SSX1 and SYT-SSX2. The presence of IGF-1 receptors in synovial sarcoma is not universal, but has been associated with higher malignancy. Pazopanib, a tyrosine-kinase inhibitor, has been approved for use in synovial sarcoma; the use of IGF-1 receptor inhibitors is undergoing clinical trials. The association of acromegaly and synovial sarcoma has not been reported so far but is plausible from an etiopathogenetic point of view. We hereby report the case of a patient presenting with a synovial sarcoma after long-standing acromegaly.

Methods

Review of the patient's records and of the relevant literature

Results (clinical case)

A 50-year-old patient complained of a painful nodule of about 3 cm in the medial epicondyle of her right elbow. After surgery the pathology diagnosis was synovial sarcoma, and the postsurgical workup only found two apparently unrelated nodules of 3 and 5 mm diameter in her right lung (CT scan). Due to the appearance of her hands, feet and nose, she was referred to our Endocrinology Clinic with the suspicion of acromegaly. The patient did not complain of any symptoms and her appearance had not substantially changed in the last ten years. Acromegaly was confirmed by high IGF-1 and lack of suppression of GH in OGTT. MEN-1 was excluded. An MR scan showed a 17 mm pituitary adenoma with minor stem displacement, not compromising the cavernous or the optic chiasm. Transsphenoidal surgery was performed, with near-normalization of plasma IGF-1, preservation of the pituitary function and no ionic disturbances; the postsurgical workup including digestive endoscopy, mammography and cardiac ultrasonography is forthcoming.

Conclusions

Both acromegaly and synovial sarcoma are infrequent, and their coincidental association is unlikely. On the other hand, acromegaly is associated with many neoplasms via IGF-1 receptor hyperactivation. Synovial sarcoma should be added to the gamut of suspected acromegalia-associated neoplasms.

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Pituitary ACTH Secreting Carcinoma or metastasized Small Cell Pulmonary Carcinoma?

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Pituitary carcinomas are rare and represent a challenge in clinical practice. Most secondary tumour localizations are intracranial and spinal, followed by liver, cervical lymph node, bone and, rarely, lung. PC frequently exhibit resistance to most usual therapies and the mean survival time is usually <4 years once metastases have been identified. Ectopic ACTH Syndrome is, in up to 50% cases, caused by lung tumours including carcinoids or Small Cell Lung Carcinomas (SCLC). SCLC can secrete ACTH in 1-6% cases. Pituitary metastasis are rare and mainly derived from breast and lung cancers. We report a case of 75 years old men with past history of hypertension, that entered the emergency room with pulmonar tromboembolism (PTE). Two days after he suffered apoplexy of a a previously unknown pituitary macroadenoma. He had elevated ACTH, urinary free cortisol, late serum night cortisol and normal abdominopelvic TC (beyond PTE lesions). He had no cushingoid features. Lab values and adenoma volume improved, but 9 months later he suddenly developed symptoms of hypercortisolism with worsening lab and imaging. He underwent transphenoidal surgery with partial removal. Immunohistochemistry revelead: ACTH adenoma with bone invasion, Ki 40%. He was reoperated and submitted to CyberKnife/SRS for residual left intracavernous adenoma in 3 months. He was clinicaly stable for 8 months, although without remission, under Metirapone therapy. Due to adenoma regrowth, a third surgery with a macroscopically extended removal was performed. Two days after he had basal cortisol 132 mg/dl and severe de novo hypokalemia. 18F-FDG PET-TC showed a suspicious lung nodule and hepatic metastasis. He maintained Metirapone and initiated Ketoconazole. The hepatic biopsy revealed neoplastic cells, Ki 90%, CK CAM5.2, Sinaptofisin, CD56 and Cromogranin A positive; CK7 and CK5/6 negative. It was assumed a probable origin in SCLC. The pulmonary biopsy revealed necrotic tissue. Pituitary histology was reviewed: Sinaptofisin positive, TTF1, napsina A and P40 negative. The results excludes pulmonary origin. Pulmonary oncology group classified the pulmonary lesion as SCLC, T3N0M1c-IVB and patient began chemotherapy with inicial clinical and pulmonar nodule improvement. Subsequent complications as pancitopenia, large haematomas, severe hypokaliemia, SARS CoV 2 infection and Klebsiella sepsis led to chemotherapy interruption and lastly patient's death. A post morten hepatic biopsy immunohistochemistry review showed TTF1 and ACTH negative. The authors conclude this is a rare case of an ACTH secreting Pituitary Carcinoma with fulminant metastatic lung and hepatic disease and highlight for the challenges and difficulties in diagnosing and treating those patients.

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AMH in men: Higher serum levels associated with healthy male aging

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Anti-Müllerian hormone (AMH), known for its role in fetal development and female reproduction, is also present in adult and elderly men in considerable amounts. In recent years, controversial findings regarding relations to age, other hormones, and BMI (possibly based on a dilutional effect due to higher blood volume) have been discussed. To date, little is known of its clinical relevance in this population. We aimed to further investigate AMH levels in an aging male population and explore their relationship to various health parameters referring to potentially underlying (patho-)physiology. Out of the ongoing prospective BioPersMed cohort (Biomarkers for Personalized Medicine), we included male volunteers with available serum AMH measurements for cross-sectional ($n=379$) and longitudinal analysis ($n=320$) analysis over 3.8 ± 1.2 (max 6.8) years. AMH and metabolic, hormonal, reproductive, and functional muscle parameters, as well as DXA-derived (dual energy X-ray absorptiometry) body

composition were explored. AMH values were log-transformed for the statistical analyses, adjusted R^2 values are given. In our cohort, median age was 59 years (IQR = 13) and median serum AMH levels ranged from 0.07 to 23 ng/ml (median = 4.75; IQR = 4.02). An initial forward stepwise linear regression model included follicle stimulating hormone (FSH), estradiol (E2), total lean mass and mean handgrip values to best explain the variance of AMH levels ($R^2 = 0.217$). There was an inverse relationship of AMH and age ($R^2 = 0.021$; $\beta = -0.004$; $P = 0.003$). In >75% of participants, AMH levels decreased during follow-up. FSH was the most powerful predictor ($R^2 = 0.159$; $\beta = -0.017$; $P < 0.0001$) of AMH. When both age and FSH were included in a model ($R^2 = 0.162$), age was no longer significant ($P = 0.153$), in contrast to FSH ($P < 0.0001$). AMH decreased with BMI ($R^2 = 0.044$; $\beta = -0.01$; $P = 0.002$), but lean mass yielded a better fit ($R^2 = 0.065$; $\beta = -0.008$; $P < 0.001$) than BMI or fat mass. Including both parameters ($R^2 = 0.062$), the relationship with BMI was no longer significant ($P = 0.7$) other than with lean mass ($\beta = -0.007$; $P = 0.006$). E2 was inversely correlated to AMH levels ($R^2 = 0.049$; $\beta = -0.003$; $P < 0.0001$), remaining significant after including potential confounders. The positive relationship of AMH and mean handgrip ($R^2 = 0.009$; $\beta = 0.001$; $P = 0.048$) stayed significant when included in a model with both lean mass and FSH ($R^2 = 0.19$; $\beta = 0.002$; $P = 0.003$). The age-dependent parameters FSH, E2, handgrip strength and lean mass were significantly related to AMH levels. Lean mass, as a proxy of blood volume, was a better predictor than BMI, suggesting some dilution effect. In summary, we found higher AMH levels being an interesting marker for healthy aging in males.

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Polycythemia vera and feminizing hormone treatment in an individual Assigned Male at Birth (AMAB): a prickly situation

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Introduction
Feminizing hormone therapy (HT) for male-assigned at birth (AMAB) includes estrogens, often in combination with anti-androgens. Several studies have reported an increased incidence of cardiovascular diseases and venous thromboembolism in AMAB receiving estrogens. Indeed, procoagulant changes induced by estrogen-based HT occur in transwomen as well as in cisgender individuals. Therefore, using estrogen in gender-affirming HT is relatively contraindicated in those with a history of thrombosis or thrombophilia. Polycythemia vera (PV) is a chronic myeloproliferative neoplasm characterized by increased erythropoiesis and is a relative contraindication to HT because of its high thrombotic risk.
Case Presentation
We describe a 36-year-old AMAB with PV and gender dysphoria. The patient had suffered clinically significant distress due to gender incongruence with a stable female gender identity since childhood. Indeed, in 2020, a diagnosis of gender dysphoria was made, and the patient expressed her firm will to begin a feminizing transition. However, in 2017, she was diagnosed with JAK2-positive PV and started treatment with low-dose aspirin and phlebotomy every month. Given her younger age and no history of thrombosis, her PV was considered at low risk for recurrent thrombosis. Nevertheless, the use of estrogen in her gender-affirming therapy was initially avoided due to the negative advice of her hematologist. Thus, to reduce her significant dysphoria, low-dose anti-androgen therapy with spironolactone 25 mg/day, preferred for less procoagulant effects, was started in June 2021 and titrated to 50 mg/day with clinical and psychological benefit. After one-year, lower testosterone levels were detected with concomitant improvement in hematocrit (43.5% vs 47.5% pre-treatment) and erythrocyte count (5.3/mm^3 vs 6.2/mm^3), allowing to extend the phlebotomy interval to 3 months.
Discussion & Conclusion
To date, there are no guidelines for gender-affirming HT in PV patients, and to our knowledge, no cases have been reported. Because of the lack of literature, we investigated the thrombosis risk of PV in other hyperestrogenic conditions, such as pregnancy. In patients with low-risk PV during pregnancy, antiplatelet therapy alone appears to be sufficient to prevent thrombotic complications. Therefore, even in our patient, low-dose aspirin helps to control the thrombotic risk. Moreover, anti-androgen therapy also had a beneficial effect by lowering the hematocrit, may be related to the decrease in testosterone levels, which normally increase erythropoietin and erythrocyte production. However, anti-androgen therapy alone could lead to hypogonadism with all its complications. Therefore, in our AMAB with PV we are currently considering combining anti-androgens with low-doses transdermal estrogens.

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A case of functional hypercortisolism associated to alcohol abuse in a 43-year-old male

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Objective
Functional hypercortisolism associated with alcohol abuse is an infrequently diagnosed entity of unknown prevalence. Ethanol elicits hypothalamic over-secretion of CRH with subsequent increase in ACTH and cortisol. It may simulate Cushing's disease both clinically and biochemically but there are no anatomic lesions and the diagnosis is confirmed by normalization of the biochemical pattern after at least 1 month of abstinence from alcohol. We hereby report a clinical case in order to increase the awareness of alcohol-induced functional hypercortisolism.
Methods
Review of the patient's record and of the relevant literature
Clinical Case
A male, 43-year-old patient was referred to our Endocrinology Clinic with suspected Cushing's syndrome, because of the typical phenotype, with central obesity and proximal muscle atrophy, round face, interscapular fat pad, violaceous striae and ecchymosis. These signs had appeared gradually during the last 5-8 years but in the last few months he complained of progressive incapacitating asthenia. The patient showed borderline central obesity (BMI 29.4 kg/m^2), with enlarged liver without palpable lumps, high blood pressure (154/92 mmHg) and inability to stand up from the sitting position without arm support Lab tests; Routine normal except fasting glucose 112 mg/dl, HbA1c 6.2%, triglycerides 368 mg/dl, AST 124 U/l, ALT 98 U/l, GGT 169 U/l, cyanocobalamin <137 pg/ml, folate 2.1 ng/ml, MCV 102 fL, platelets 127000/mm^3, FIB-4 index 4.73. Hormones: Normal except ACTH 57.2 pg/ml, fasting cortisol after 1 mg dexamethasone suppression 18.1 µg/dl; 24-hour cortisol excretion 211 µg. After 14 days the results were similar (61.4 pg/ml, 21.8 µg/dl, 198 µg respectively). Abdominal ultrasonography: hepatomegaly and intense steatosis without nodules: both adrenals were normal. Pituitary MRI was normal. Thoracic/abdominal CT showed no additional findings Petrosal sinus sampling was scheduled but then the patient revealed alcohol abuse for the last 10 years, with usual daily intake of half a liter of rum plus variable amounts of beer, wine and other spirits. The patient was encouraged to abstain from alcohol and treated with vitamin B complex supplements. After 3 months, the Cushing phenotype was largely reversed, the patient could stand up easily, and the biochemical profile was normal (cortisol 1.4 µg/dl after dexamethasone, excretion 32 µg, fasting ACTH 26 pg/ml).
Conclusions
This case illustrates a probably underdiagnosed entity. Alcohol abuse may go unreported and patients may remain in a diagnostic quagmire. When hypercortisolism is unexplained, functional causes such as alcohol abuse, major depression, chronic emotional stress, etc. must be ruled out.

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Insulin Pump Therapy in Pregnant Women with type 1 Diabetes: Flash Glucose Monitoring vs Sensor Augmented Pump

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Objectives
Pregnant women with type 1 diabetes (T1D) are associated with an increased risk of maternal fetal complications. Continuous subcutaneous insulin infusion [CSII] has been shown to improve metabolic control and perinatal morbidity. Few studies have compared the use of CSII with SAP (sensor augmented pump) therapy to flash glucose monitoring (FSL) in pregnant women with T1D. We aim to evaluate the possible differences between both monitoring systems associated with CSII therapy and assess their effect on metabolic control during pregnancy and maternal-fetal morbidity.
Methods
This retrospective cohort study enrolled pregnant women with T1D on CSII treatment at a tertiary hospital between 2018 and 2022. We compared the SAP system (640G pump) with FSL monitoring (ISCI-FSL). Glucometric data of 14 days were obtained at every trimester of pregnancy from the different platforms (Carelink and Libreview); clinical and analytical data were obtained from medical records.
Results
were included 31 pregnant women with a mean age of 35 years and 20 years of T1D evolution. The SAP group ($n=21$) presented a higher percentage of pre-pregnancy control (80% vs 95.2%) and severe hypoglycemia in the 2 years prior to pregnancy (0 vs 28.6%), without significant differences ($P>0,05$). Regarding glycemic control, a longer time under range (<63 mg/dl) was evidenced in the ISCI-FSL group, both in the second (9.7 vs 5.8%, $P=0.044$) and in the third trimester (12.1 vs 5.6%, $P=0.012$), without statistically significant differences in time in range (63-140 mg/dl; 1stTrim 52.8 vs 54.8%, 2ndTrim 52.5 vs 55%, 3rdTrim 61.5 vs 63.9%) or in time over range (>140 mg/dl; 1st Trim 35.8 vs 36.6%, 2ndTrim 37.8 vs 39.2%, 3rd Quarter 26.4 vs 30.5%) between both groups. There were also no differences in HbA1c nor in the rate of severe hypoglycemia by trimester (table). Regarding neonatal complications, no significant differences were found in the incidence of macrosomia, neonatal hypoglycemia, malformations, and perinatal mortality, nor in the rate of maternal complications between both groups.
Conclusions
In this cohort of pregnant women with T1D on CSII therapy, FSL monitoring showed a longer time in hypoglycemia compared to the use of SAP, without finding other differences in metabolic control nor in maternal-fetal complications.

	ISCI-FSL($n=10$)	SAP($n=21$)	*P*
HbA_{1c} 1stTrim (%)	6,3 ± 0,65	6,29 ± 0,58	0,984
HbA_{1c} 2ndTrim (%)	5,94 ± 0,49	5,95 ± 0,49	0,948
HbA_{1c} 3rdTrim (%)	6,17 ± 0,56	6,24 ± 0,56	0,642
Severe hypoglycemia (%)	10	19	0,312

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Does the 'obesity paradox' have an expiration date? A bigdata retrospective cohort

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Background
Although obesity and overweight are associated with increased morbidity and mortality, higher body mass index (BMI) has been shown to be a protective factor from mortality in patients with acute infectious disease, also known as the 'obesity paradox'. However, it is unknown whether these effects persist at long-term follow-up.
Objective
To investigate the relationship between BMI and mortality after hospitalization with an infectious disease in a five-year follow-up period.
Methods
A retrospective analysis of 25,226 adult patients admitted with an acute infectious disease between the years 2010-2020 to Shamir Medical Center, Israel, was conducted. We compared patients in the following BMI categories underweight 15-18.5 kg/m^2, normal-weight 18.5-25 kg/m^2, overweight 25-30 kg/m^2, obesity class-I 30-35 kg/m^2, obesity class-II 35-40 kg/m^2, and obesity class-III 40-45 kg/m^2, regarding mortality during hospitalization and follow-up.
Results
Patients in different BMI categories were heterogeneous regarding baseline demographics and comorbidities, as well as infectious syndrome at index hospitalization. In-hospital mortality and one-year mortality were higher in underweight and normal-weight patients as compared to all other categories, 22% and 13.2% vs. 7-9% ($P<0.001$) in-hospital, and 31.8% and 20.6% vs. 13-15.6% ($P<0.001$) at one year. Five-year mortality was only significantly higher in the underweight group, 44.4% vs. 30.8%-36.1% ($P<0.001$). In a multivariable logistic regression analysis, adjusted for age, sex, comorbidities, and infectious syndrome, underweight was associated with a significantly increased odds ratio (OR) for In-hospital, one-year, and five-year mortality. While, overweight and obesity were associated with a decreased OR for mortality at all time points. Compared to normal-weight OR for mortality at five years was 0.68 (CI 0.62-0.74 $P<0.001$) in the overweight category, 0.61 (CI 0.55-0.68, $P<0.001$) in obesity class I, 0.71 (CI 0.61-0.83, $P<0.001$) in obesity class II, and 0.71 (CI 0.56-0.89, $P=0.004$) in obesity class III. In a survival analysis model, all categories of obesity were associated with a decreased OR for mortality compared to normal weight, while underweight was associated with increased OR (five-year mortality OR 1.72 CI 1.59-2.07, $P<0.001$).
Conclusions
Our study found evidence of an 'obesity paradox' for up to five years following hospitalization due to infectious causes. Although we did not find a significant univariate association between BMI of 18.5-25 kg/m^2 and five-year mortality, upon multivariate analysis all groups of overweight and obesity were independently associated with decreased mortality compared to this group. Further studies should search for explanations for this counterintuitive phenomenon.

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Reduction of urinary albumin excretion with empagliflozin in patients with type 2 diabetes and uncontrolled hypertension

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Introduction
Empagliflozin has a well-established anti-albuminuric effect in patients with T2DM, but in almost all available trials the baseline blood pressure was well controlled with SB $P<140$ mmHg. We analyzed the impact of empagliflozin treatment in patients with T2DM and uncontrolled hypertension, and its relationship with the changes in HbA1c and SBP.
Methods
Retrospective analysis of the albuminuria, SBP and HbA1c data in patients with T2DM and high office blood pressure (SB $P>140$ mmHg) when starting empagliflozin therapy. Post-hoc mediation analyses were performed with SBP and HbA1c changes as mediators in order to quantify their relative contributions to the changes in albuminuria. All included patients gave informed consent. Patients who started or changed antihypertensive medication simultaneously with the onset of empagliflozin therapy were excluded. Data are given as mean ± sd.
Results
Data were obtained from 169 patients (59.8% women, age 64.5 ± 9.3 years) in the visit in which empagliflozin was started (10 mg day in almost all cases), and in a successive visit after 3-6 months. 101 patients were on ACEI or ARB (59.7%). Baseline HbA1c was 8.2 ± 1.6% and the change was -0.7 ± 0.3% ($P=0.011$, paired t-test). Baseline SBP was 167 ± 18 mmHg and the change was 7.3 ± 5.1 mmHg ($P=0.007$, paired t-test). At baseline, 83 (49%), 57 (34%) and 29 (17%);

and successively 98 (58%), 48 (28%) and 23 (14%) had normoalbuminuria (<30 mg/g Cr), microalbuminuria (30-300 mg/g Cr) or macroalbuminuria (> 300 mg/g Cr), respectively. Albuminuria was reduced by 9% (CI 95%: 14%-4%, $P=0.043$) in patients with normoalbuminuria; by 29% (35%-23%, $P=0.002$) in patients with microalbuminuria, and by 38% (47%-29%, $P=0.003$) in patients with macroalbuminuria. The reduction in albuminuria was significantly correlated with those of HbA1c (Pearson's R: 0.18; $P=0.008$) and SBP (Pearson's R 0.26; $P=0.003$). Mediation analyses showed that 16% (CI 95%: 12-20%, $P=0.011$) of the reduction in albuminuria was mediated by HbA1c reduction, and 25% (19-31%, $P=0.004$) by SBP reduction, but 59% was independent of both mediators.
Conclusions
Empagliflozin therapy was associated with a clinically and statistically significant reduction in albuminuria in patients with T2DM and uncontrolled hypertension. Although the reductions in HbA1c and SBP clearly contributed to this effect, much of the reduction in albuminuria seems to be attributable to other mechanisms, most likely the restoration of the tubuloglomerular feedback.

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Retinal quantitative traits as prognostic factors for diabetic cardiomyopathy in people with type 2 diabetes: A scoping review

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Introduction
Heart failure (HF) morbidity and mortality are increasing at an alarming rate in people with type 2 diabetes (T2D). Myocardial dysfunction may develop without ischemic heart disease (IHD), hypertension, or valvular pathologies, and which is defined as diabetic cardiomyopathy (DCM). Although the pathophysiology of DCM is unclear, DCM is initially characterised by myocardial fibrosis, dysfunctional remodelling, and associated diastolic dysfunction, later by systolic dysfunction, and eventually by clinical HF. Retinal quantitative traits have been seen associated with cardiovascular complications in T2D. Previous studies have shown that the presence of narrowing retinal arterioles and decreased fractal dimension – a novel biomarker of microvascular density- have been associated with IHD and HF, independent of well-known cardiovascular (CV) risk factors. A novel paradigm of DCM focuses on pro inflammatory signalling originating from the myocardial microvasculature. Nevertheless, phenotyping the cardiac microvasculature in this population is not feasible in clinical settings. In comparison, the retinal microvasculature can be completely noninvasively and reproducibly evaluated. Currently, there is a paucity about the current evidence about retinal traits and DCM. This scoping review aims to map existing literature and provide a summary of retinal parameters and DCM in people with T2D. This includes risk factors, interventions and identification of research gaps in the literature.
Methods
Electronic databases (MEDLINE, EMBASE, and, Web of Science) were systematically and independently searched following the Joanna Briggs Institute (JBI) guidelines until February 2023. Two independent researchers assessed the literature and conducted the review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines for Scoping Reviews (PRISMA-ScR).
Results
Of the 1072 articles screened, 15 articles met inclusion criteria. The majority were cross-sectional and prospective studies concentrated in North America and Europe. In people with T2D, the presence of moderate and severe retinopathy was associated with heart failure and subclinical left ventricular myocardial dysfunction. Moreover, low retinal vascular fractal dimension was associated with congestive heart failure.
Conclusion
There has been much optimism that quantitative retinal traits may associate with diabetic cardiomyopathy beyond conventional CV risk factors. However, evidence is scarce in people with T2D compared to population-based studies. Clearly, further studies are necessary to understand the potential phenotypes including echocardiographic findings and underlying mechanisms for DCM in people with T2D.

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Effects of oral semaglutide on the lipid profile of patients with type 2 diabetes mellitus and obesity: Are they mediated by body weight loss?

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Introduction
It has been reported that patients with obesity and T2DM treated with oral semaglutide not only have a reduced total caloric input, but they also tend to reduce the proportion of fatty and sweet foodstuffs in an *ad libitum* diet. A modest improvement in the lipid profile of patients with obesity and T2DM treated with oral semaglutide has been reported, but its dependence on weight loss is not well established. We undertook to study the mediation effect of weight loss on the lipid profile changes in these patients.
Methods
We performed retrospective analyses of the lipid profiles of consecutive patients with obesity and T2DM who started oral semaglutide therapy. Data were obtained from the baseline visit and a successive visit, 3-5 months afterwards. Post-hoc mediation analyses were performed in order to quantify the relative contribution of weight loss in the lipid profile changes. Patients who started or changed lipid-lowering medication simultaneously, or refused informed consent were excluded. Data are given as mean $\pm$ sd.
Results
Data were obtained from 48 patients, 31 (65%) women, age 54.4 $\pm$ 11.8 years, T2DM duration 6.7 $\pm$ 2.7 years, BMI 36.6 $\pm$ 5.3 kg/m^2; 43 (90%) had 14 mg semaglutide daily, 3 (6%) 7 mg, and 2 (4%) 3 mg. 29 (60%) of the patents were on statins,12 (25%) on fibrates and 4 (8%) on EPA/DHA supplements. The geometric mean of the total cholesterolemia at baseline was 167 mg/dl, variation coefficient 47%. For HDLc, LDLc and non-HDLc the values were 44 mg/dl, 58%; 82 mg/dl, 49%; 122 mg/dl, 52%, and 207 mg/dl, 68%. The changes in total cholesterol and its fractions (HDLc, LDLc, non-HDLc) were favorable but non-significant (-4.8%, +2,2%, -7.3%, -2.1%) while there was a significant reduction of triglyceridemia from its baseline value 207 $\pm$ 68 mg/dl (-17.6 $\pm$ 11.5%, $P=0.021$). The weight loss was -3.6 $\pm$ 1.5 kg ($P=0.033$). The reductions in weight and triglycerides were positively correlated (Pearson's R: 0.29, $P=0.0023$). The mediation analyses showed that a reduction of 6.4 $\pm$ 7.3% in triglyceridemia was mediated by weight loss, but 11.2 $\pm$ 8.4% was independent of it.
Conclusions
In patients with T2DM and obesity, oral semaglutide significantly improved plasma triglycerides, with a non-significant improvement of total cholesterol and its fractions. The reduction of triglyceridemia was mediated only partially by weight loss, suggesting additional mechanisms, maybe including healthier dietary choices. Oral semaglutide may reduce the need for fibrates and EPA/DHA supplements.

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P809

Somatostatin Analogues or Active Surveillance in Sporadic and MEN1 associated Non-functioning Pancreatic Neuroendocrine Tumors

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Introduction
Non-functioning (NF), sporadic and MEN1 associated, G1-G2 pancreatic neuroendocrine tumors (PanNETs) usually display an indolent course. Surgery

is the first-choice treatment for localized tumors >2 cm. Unresectable or metastatic PanNETs expressing somatostatin receptors (SSTRs) are treated with somatostatin analogs (SSAs). The standard treatment for patients with PanNETs ≤ 2 cm is active surveillance (AS). Yet no evidence of the value of SSA treatment exist in such patient population.
Aim(s)
To assess the clinical value of SSAs in patients with PanNETs ≤ 2 cm. Material and methods: Data from patients (pts) NF, G1-G2 PanNETs≤ 2 cm were retrospectively collected. Median progression-free survival (mPFS) and response rate (RR) were analyzed in SSA group and AS group. Results: From June 2007 to June 2022, data from 46 pts were considered: 29 pts, who declined an AS program but had not indication for surgery, entered in the SSA group (21 sporadic and 8 MEN1 associatd PanNET) and 17 in the AS group. At a median follow-up of 64.8 months for sporadic and of 63.9 for MEN1 associated PanNET, no disease progression (PD) was reported in the SSA group, without differences between sporadic and MEN1 associated PanNET. While the PD rate was 23.5 % in the AS group, with a mPFS of 36.2 months.
Conclusion
SSAs therapy showed significant antiproliferative activity in patients with both sporadic and MEN1 associated NF, G1-G2 PanNETs ≤ 2 cm. SSAs treatment delay tumor progression and distant spread in small lesions that sometimes may reveal an unpredictable aggressiveness.

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P810

Evaluation with Dynamic Contrast Enhancement (DCE)-MRI in Patients with Acromegaly

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Acromegaly is a rare disease with high morbidity and mortality associated with excessive secretion of growth hormone due to adenoma of somatotroph cells in the pituitary gland. In patients with acromegaly, residue may remain after surgical treatment, and disease control is attempted with surgery, medical treatment or radiotherapy for these patients. Pituitary imaging, IGF-1 and GH measurement are used in the follow-ups. Dynamic Contrast Enhancement perfusion MRI provides information about tissue properties at the microvascular level. It provides information and comparison about normal-neoplastic tissue permeability. K-trans transfer constant and increases in neovascularity The K-trans demonstrated by this MRI is the transfer constant and increases in neovascularity. Ve indicates the fractional volume of the extracellular space, increasing in necrosis. Kep is the velocity constant. The IAUC is a data on the interstitial area under curve, fractional blood volume. Since there are also studies showing that GH increases neovascularity, we thought that evaluation with Dynamic Contrast Enhancement (DCE)-MRI could be a clearer guide to the clinician in terms of clarifying the adenoma type during the diagnosis and follow-up of patients with acromegaly.
Material Method
A total of 31 patients including postoperative residual adenoma, 16 diagnosed with non-functioning adenoma (NFA), and 15 diagnosed with acromegaly, were included in the study. MRI Examination was performed with a GE 750W 3.0T MR scanner (2013, GE Healthcare, Milwaukee, WI) using a 16-channel GEM Quiet HNU head coil. Precontrast sagittal and coronal T1 and T2 weighted, postcontrast coronal coronal and sagittal T1, coronal FIESTA sequences after DCE-MRI were taken. MRI images were evaluated by a radiologist with 20 years of experience in neuroradiology. The radiologist was blind to the patients' pathology.
Results
Although the K-transAdenoma and KepAdenoma values were higher in the patients' residual adenomas, the madian values were higher in the acromegaly residues, but no statistically significant difference was found ($P>0.05$). However, a positive correlation was found between the GH values of GH secreting adenomas and K-transAdenoma and KepAdenoma values ($r=0.552$, $r=0.605$, $P<0.05$, respectively).
Discussion
DCE-MRI may be a promising method in the diagnosis and follow-up of acromegaly, since the median values are high in acromegaly residues, although there is no statistical difference, and there is also a positive correlation between GH levels and Ktrans and Kep values in GH-secreting adenomas. Considering the available data together with the relationship between GH and neovascularization, it seems promising to carry out further studies by enlarging the sample.

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P811

Comparison of Metyrapone, OSilodrostat and KEToconazolE in the short-term thERapy of endogenous Cushing's syndrome: preliminary results of the MOSKETEER study

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Background
Steroid synthesis inhibitors, like metyrapone, osilodrostat, and ketoconazole are used as second-line treatment in all types of endogenous Cushing's syndrome (CS). However, a direct comparison of these three drugs is missing. This study aimed to compare these drugs in the short-term therapy of CS.
Design
Retrospective multicenter study involving 15 European centers.
Methods
Patients with CS treated with metyrapone, osilodrostat or ketoconazole as monotherapy for at least 2 weeks were considered eligible. Main outcomes were changes in serum cortisol and 24h urinary free cortisol (24h-UFC) after 2 (T1), 4 (T2), and 12 weeks (T3) of therapy compared to baseline (T0), evaluated as delta (change) percentage from T0 to the different time points. A mixed model was used to explore the data.
Results
Data of 210 patients from 9/15 centers were available. Of the 210 patients (78% females), 158 (75 %) suffered from ACTH-dependent and 52 (25%) from ACTH-independent CS. 83 (40%) patients were treated with metyrapone, 78 (37%) with osilodrostat and 49 (23%) with ketoconazole. No difference in terms of CS subtypes ($P=0.19$) and baseline 24h-UFC (median 295.5µg/24h, 286.0µg/24h and 360.0µg/24h for metyrapone, osilodrostat and ketoconazole, respectively, $P=0.32$) was identified. Median daily starting doses were 750 (range 250-2000)mg, 2 (1-10)mg and 400 (200-800)mg for metyrapone, osilodrostat and ketoconazole, which increased during the treatment for all drugs up to 1000 (250-3000)mg, 5 (1-40)mg and 400 (200-1200)mg, respectively (all $P<0.05$). 24h-UFC significantly decreased in all time points only in the osilodrostat group (-34% in T1, -46% in T2, and -68% in T3, $P<0.001$), being more pronounced at T3 than metyrapone (-37%, $P=0.02$). Under ketoconazole 24h-UFC decreased of -48% at T3. A decrease in serum cortisol was observed at T3 in all groups (metyrapone -7.8%; osilodrostat -39%; ketoconazole -36%). At T3 no significant changes in potassium levels were identified (metyrapone 0%; osilodrostat +2%; ketoconazole -0.6%); and 7 (15%) patients under metyrapone, 6 (10%) under osilodrostat and 0 under ketoconazole were supplemented ($P=0.03$ per trend). At T1, a decrease in

number of antihypertensives was identified in 10% of patients under metyrapone, 22% under osilodrostat and 6% under ketoconazole ($P=0.006$), whereas at T2 and T3 no significant differences were identified. No significant change was observed in Hb1Ac(%).

Conclusion

These preliminary results confirmed the efficacy of all the three drugs in decreasing hypercortisolism. Osilodrostat might act faster in decreasing blood pressure. However, these preliminary results need to be validated in the final cohort.

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P812

Importance of HLA in Grave's orbitopathy development in Caucasian population

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Introduction

Graves' disease (GD), similarly to most autoimmune disease, is triggered by environmental factors in genetically predisposed individuals. Particular HLA alleles increase or decrease GD risk. We have recently demonstrated novel, previously not reported association between a presence of alleles *HLA-B*39:06, -B*37:01, -C*14:02, -C*03:02, -C*17:01, -DRB1*14:01* and GD. These alleles are independent risk factors, with no linkage disequilibrium with other, already reported, high-risk alleles. Up to 2022, no such correlation was demonstrated for Graves' orbitopathy (GO) in Caucasian population.

Material and Methods

We performed *HLA-A, -B, -C, -DQB1* and *-DRB1* genotyping using a high-resolution next generation sequencing method in a total number of 2378 persons including 70 patients with GO, 91 patients with non-GO GD and 2217 healthy controls to compare allele frequencies in GO, non-GO and control groups.

Results

The risk of GO was significantly associated with a presence of *HLA-A*01:01, -A*32:01, -B*37:01, -B*39:01, -B*42:01, -C*08:02, C*03:02, DRB1*03:01, DRB1*14:01* and *DQB1*02:01*. The highest risk of GO was associated with the presence of *HLA-C*08:02* (OR 6.9), *-C*03:02* (8.3), *-DRB1*14:01* (6.2) and *-B*37:01* (OR 4.5). On the other hand, *HLA-C*04:01, -C*03:04, -C*07:02* and *-DRB1*15:02* were demonstrated to be protective alleles. Moreover, correlations between HLA alleles and increased or decreased risk of non-GO GD, but with no impact on risk of GO development, were revealed. The presence of *HLA-B*08:01, -B*39:06, -B*51:01, -C*07:01, -C*14:02, -C*16:02, -C*17:01, -DRB1*01:03, -DRB1*15:02, -DQB1*03:01* was associated with increased risk of non-GO GD, while *HLA-B*07:02, -C*07:02, -A*32:01* were demonstrated to be protective against non-GO GD. The highest risk of non-GO was associated with the presence of *HLA-DRB1*01:03* (OR 8.4), *-B*39:06* (OR 5.6), *-C*17:01* (OR 4.6) and *-C*16:02* (OR 4.2). Additionally, correlations between HLA and clinical risk of GO were found.

Conclusions

These results complemented our previous study, which demonstrated GD high risk alleles, by precise identification and distinction of the groups of GO-related and GO-protective alleles, as well as the alleles strongly related to non-GO GD. The knowledge on HLA-related genetic background of GO and non-GO GD constitutes an important step in a development of personalized medicine, with new possibilities of individual risk assessment and patient-tailored treatment.

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P813

Subacute thyroiditis development and its clinical course are HLA-dependent

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Introduction

Subacute thyroiditis is a thyroid inflammatory disease, triggered mainly by viral factors in genetically susceptible individuals. Up to 2020, only HLA-B*35 was confirmed as SAT-related. However, obviously in HLA-B*35-negative patients, some other genetic background occurs.

Material and Methods

We performed HLA-typing using high resolution NGS method in different groups of patients with SAT and demonstrated the new association between HLA and SAT in the Caucasian population.

Results

In addition to *HLA-B*35*, SAT was proved to be associated with the presence of *HLA-B*18:01, -DRB1*01* and *-C*04:01*. In Caucasians, *HLA-C*04:01* is in a linkage disequilibrium with *HLA-B*35:01/02/03*. Therefore, *HLA-C*04:01* alone cannot be treated as an independent SAT risk factor due to its linkage with the previously described *HLA-B*35*. However, the presence of any of the two haplotypes should be considered as a marker of genetic susceptibility to SAT. No such linkage disequilibrium has been described for *HLA-B*18:01* or *-DRB1*01* so these alleles should be considered new, completely independent SAT risk factors. Moreover, clinical course of SAT also seemed to be HLA-dependent. In regard to US pattern, typically observed multiple hypoechoic blurred lesions were demonstrated to be rarely found in *-B*18:01*-positive patients. In most cases with *HLA-B*18:01* only, unilateral homogenously hypoechoic single SAT area, filling the whole affected lobe and mimicking the large thyroid nodule was observed. This report explained the phenomenon of various US patterns of SAT. Additionally, the risk of SAT recurrence was also reported to be HLA-associated and was significantly higher in patients with co-presence of *HLA-B*18:01* and *-B*35*. In such cases, the steroid treatment should be intensified with slower dose reduction. SARS-CoV-2 is a novel pathogen which can trigger SAT. On the contrary to other viral factors, SAT onset in COVID-19 can be very rapid, and even simultaneous presence of both diseases was described. Our study revealed that this phenomenon can be related to the presence of homozygosity at *HLA-B*35*. COVID-19 vaccination is also a new factor which can induce SAT. We postulated that SAT occurrence after COVID-19 vaccination can be related to a co-presence of *HLA-B*35:03* and *-C*04:01*.

Conclusions

Our study provided the set of four alleles whose assessment allows confirming the genetic predisposition for SAT in almost all patients. HLA-related background seems to play a crucial role in SAT occurrence as well as its typical of atypical clinical course, including cases induced by SARS-CoV-2 and COVID-19 vaccination.

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P814

Is Patient Anxiety A Risk Factor for FNAB Sample Adequacy?

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Aim

Currently, imaging tools are increasing the frequency of thyroid nodules to 50%, and thyroid cancer risk is 7-15%. The most cost-effective, accurate diagnosis method is fine-needle aspiration biopsy (FNAB). However, non-diagnostic (ND) results can delay diagnosis, cause different procedures, raise costs, and distress patients. In addition, FNAB sample adequacy is affected by advanced age, nodule size (<5-10mm), cystic dominating nodules, macrocalcification, and hypo-echogenicity. We aimed to see if situational anxiety was linked to non-diagnostic cytology.

Methods

The prospective cross-sectional study included patients who underwent thyroid fine-needle aspiration at the Endocrinology Clinic of Sultan Abdulhamid Training and Research Hospital between 11/2022 and 02/2023. The State-Trait Anxiety Inventory (STAI) questionnaire and visual analog scale (VAS) for pain assessed situational anxiety and pain in patients just before the procedure. We tested whether the STAI-S score is related to non-diagnostic results.

Results

Of the 119 patients included in the study, 98 were female, and 21 were male. 25 (21%) nodules were non-diagnostic. We divided patients into two groups according to the cytology results: non-diagnostic and others. According to the groups, STAI and VAS scores and other demographic characteristics are given in Table 1. A statistically significant relation was found between the patient's STAI-S score and VAS score and the cytology result of non-diagnostic thyroid nodules ($P=$ 0.001 and $P=0.008$). When we examined the factors associated with the non-diagnostic outcome in multivariate logistic regression analysis, the STAI-S score was found to be again associated with the non-diagnostic outcome. (OR = 1.069, $P=0.02$)

Table 1. Characteristics of the patients, STAI, and VAS scores

Parameters	All patients	Non-diagnostic group	Others	P value
Number of patients	119	25	94	
Age(years)	54.86±12.2	58.64±12.05	53.86±12.15	0,087
Gender(n)				0,38
F	98	19	79	
M	21	6	15	
STAI-S	47.31±12.37	54,80±13.42	45.31±11.34	**0,001**
VAS	2.57±1.51	3(1-6)	2(1-6)	**0,008**
Nodule size(mm)	21.70±0.72	21.60±8.45	21.73±7.68	0.94
Architecture (cyst/solid)	26/93	8/17	18/76	0.16
Boundary (regular/irregular)	18/101	3/22	15/79	0.44
Echogenicity (hypo/iso)	61/58	15/10	46/48	0.37
Macrocalcification (absent/present)	19/100	5/25	14/80	0.54

F: Female, M: Male, STAI-S: Situational State-Trait Anxiety Inventory, VAS: visual analog scale. Independent-Samples T (2 variables) test was used for parametric variables, and data were given as mean±SD. Mann-Whitney test was used for non-parametric variables, and data were shared median (minimum-maximum).

Conclusions

Hence, anxiety level and pain perception during FNAB may be risk factors for non-diagnostic cytology. Reducing anxiety and pain may decrease the incidence of non-diagnostic outcomes.

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P815

Abstract withdrawn

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ePoster Presentations

Adrenal and Cardiovascular Endocrinology

EP1

Adrenal Haemorrhages: A review of cases presenting to University Hospital Southampton over six-year period

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Introduction
Adrenal haemorrhage (AH) carries high mortality and morbidity. It can be unilateral or bilateral (BAH), trauma or non-trauma (NT) related. The predisposing factors include adrenal tumours, anticoagulation, thrombocytopenia, sepsis, thromboembolic disease, pregnancy, liver transplant and vaccine-induced-immune-thrombocytopenia-and-thrombosis. BAH can result in an adrenal crisis in up to 15%. BAH is usually associated with conditions contributing to adrenal vein spasm or thrombosis.
Aim
The aim of this project was to review management, causes, outcomes and follow-up in patients presenting with AH in our organization between 2017-2022.
Results
We identified 21 patients with AH during this period. Age 19-93 y, mean- 57 y, 19% $<$ 30 y, 52% $>$60 y, 62% males. 20 presented acutely, with one diagnosed electively. 20 were managed conservatively, and 1 required bleeding adrenal artery embolization. 14/21 (66.7%) were non-traumatic, 7/21 (33.3%) were trauma related. 4/21 were bilateral, and 17/21 (81%) were unilateral with slight right-sided predominance. All traumatic bleeds were unilateral. 4/21 bled into a pre-existing adrenal pathology (3/4 adenoma, 1/4 18 cm myelolipoma), 9/21 had other identifiable risk factors or their combinations (3 antiplatelets, 3 antic-oagulation, 6 hypertension, 1 vasculitis, 1 Ehlers Danlos + cocaine, 1 pregnancy, 1 sepsis, 1 diabetes ketoacidosis). All 4 BAH were non-traumatic. Severe hypertension 180-200 mmHg in 3/4 and sepsis from ischaemic foot in 1/4 were the precipitants. 7 required ITU admission, 1 had cardiac arrest, 6 were severely hypertensive (BP $>$180 mmHg), and 2 patients died during admission. 6 cases had profound hypotension on admission (5/6 unilateral, 1/6 bilateral), 2/6 had cortisol checked, and one received Hydrocortisone. Hyponatremia (range 125-133 mmol/l) was noted in 4 cases (19%) and in 50% of BAH. 3 tested for hypoadrenalism, and 2 received Hydrocortisone. 5/21 had cortisol checked, and 4/21 were covered with Hydrocortisone. 7/21 had metanephrines checked, 11/21 patients were referred to the adrenal MDT and 14 had interval imaging during follow-up.
Discussion
The single adrenal vein draining the highly vascular glands makes them sensitive to venous pressure changes and subsequent haemorrhage. Our review demonstrated high prevalence of underlying adrenal pathology and precipitating factors, mainly hypertension, anticoagulants and procoagulant states as main precipitants for NT adrenal bleeds. We observed that testing for adrenal insufficiency and steroid cover in patients with AH could be improved by admitting teams, predominantly in those requiring ITU, those with BAH, and with associated hyponatremia and hypotension. Our aim is to ensure that all patients with AH receive Endocrine input and are tested for potential adrenal insufficiency.

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EP2

A Case of Ectopic Adrenocortical Cancer Originating from the Pancreas

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Background
Ectopic malignancies arising from adrenal rests are extremely rare. Localization has been reported in the retroperitoneum, testis/scrotum, ovary, kidney, anterior abdominal wall, spinal cord, and liver associated with embryological development [1-3].
Objective
This report presents a case of ectopic adrenocortical cancer (ACC) localized to the pancreas. An exciting feature of the case was the simultaneous presence of breast cancer.
Case
A 57 years old female patient was diagnosed with mixed-type breast cancer (lobular and ductal carcinoma) in 2019. After the diagnosis, in addition to the malignant mass in the left breast on CT and FDG PET CT images, a second tumor with well-circumscribed, necrotic, heterogeneous malignant appearance was seen adjacent to the pancreas, in the left paraaortic area, without significant invasion to the environment (SUVmax: 37.7 on FDG PET CT). On abdominal MRI, A 5.2 cm diameter mass with cystic, solid components originating from the pancreatic body and tail junction, growing to posterior and inferior, was observed. The patient did not have features suggestive of hormonal hyperfunction, such as hypertension, electrolyte imbalance, cushingoid appearance, and signs of hyperandrogenism. After the lumpectomy, the mass adjacent to the pancreas was surgically removed. Positive staining with Steroidogenic factor 1 (SF1) was observed in pathology. Ki67 proliferation index was determined as 5%. Neither venous invasion nor capsular invasion was observed. This neoplasm had a diffuse pattern, increased mitosis, and marked nuclear pleomorphism. Regarding p53 mutation in tumor, 5% weak-moderate staining was observed. The tumor was diagnosed with oncocytic-type adrenocortical carcinoma. Mitotane and glucocorticoid replace-ment were added to her follow-up treatment. There was no evidence of recurrence or metastasis in the follow-ups.
Conclusion
This rare case is the first whose ectopic adrenocortical cancer is located in the pancreas. Adrenocortical cancers should also be considered in tumors of non-adrenal areas.
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EP3

A rare case of slowly progressing myopathy of unknown origin in a patient with Autoimmune polyglandular syndrome type 1 (APS-1)

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We report a 53-year-old man. At age 3, the patient was diagnosed with chronic mucocutaneous candidiasis. At age 41 the patient started losing all hair on the body with total boldness. At age 43, he first complained of muscle weakness resulting in difficulty walking, back pain and difficulties holding his head in an upright position. At age 49, he was diagnosed with chronic primary adrenal insufficiency and hypoparathyroidism. Genetic analysis confirmed APS-1 (c.769C$>$T p.R257X mutation in the AIRE gene). The patient received therapy with hydrocortisone 35 mg/day, fludrocortisone 0.5 mg/day, alfacalcidol 0.75-1 mg/day, colecalciferol 15,000 IU/week. On this treatment he had calcium levels within the reference range and no clinical signs of either hyper- or hypocortisolism. However, his muscle weakness gradually, although painlessly, progressed. At age 49 electroneuromyography showed signs of primary muscle damage: high-amplitude motor unit potentials and the absence of spontaneous muscle fiber activity were recorded. According to the results of a PET, specific metabolically active tissue was not identified, but there were described signs of atrophy of the paravertebral muscles, the left lumbar major muscle, and the gluteal muscles on both sides. There was a gradual progression in muscle weakness over time leading to serious difficulties in walking and the ability to maintain his head in the upright position (Fig1). The results of densitometry in the "Total Body" mode show signs of muscle atrophy: limb muscle mass–16793 g (normal range for men $>$19750 g), Baumgarten skeletal muscle index–6.24 kg/m^2 (normal range for men $>$7.26). According to the most recent laboratory tests, an increase in the level of creatine phosphokinase to 411 U/l (normal range, 30-200 U/l), C-reactive protein to 9.8 mg/l (normal range, 0.1-5 mg/l) were detected. Grip strength measurements showed normal performance. When hydrocortisone was replaced with prednisolone, the level of creatine phospho-kinase decreased to 184 U/l, and C-reactive protein decreased to 2 mg/l. No current evidence was found in favor of autoimmune damage to muscle tissue and no other muscle disease was detected.
Conclusion
The clinical case outlines a rare combination of APS-1 and central muscle atrophy of unknown origin, but probably related to mutation in the AIRE gene.

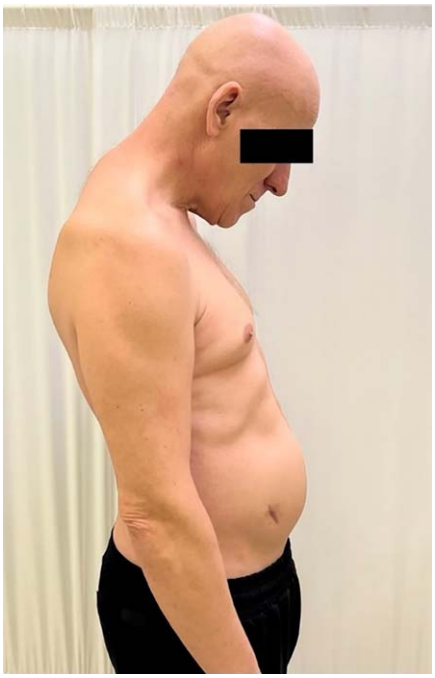

Figure 1. Involuntary position of the patient associated with atrophy of the vertebral muscles

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EP4

A case report of a single patient with a dual-functioning incidental adrenal tumor

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Introduction
An undefined lesion detected by imaging methods in one or both adrenals is known as an incidentaloma. The size and capacity of the secretion are evaluated to determine its definitive management. It is extremely uncommon for a mixed adrenal incidentaloma to appear with elevated cortisol and medullar hormone output.
Case report
A 21-year-old woman was admitted to the hospital with intermittent palpitations, headaches, and chest pain. She was already receiving medication for her diabetes and hypertension. The Cushing syndrome symptoms ('moon-face', 'lemon-on-sticks'), with a BMI of 25 kg/m^2, a BP of 140/90 mmHg, and a PR of 75/min, were found during the examination. There was no history of hirsutism, menstruation irregularity, or fractured bones.
Results
Hematology and biochemistry tests, in addition to U&E, were routine. Following a thorough wash-out, additional laboratory tests revealed non-suppressible morning serum cortisol in ODST and HDDT. The levels of dopamine, epinephrine, norepinephrine, and 24-hour urine metanephrines were all increased, as well as the serum CgA. An abdominal MDCT showed a normal left adrenal gland and an enlarged right adrenal gland (36.4×30 mm). No abnormal findings were detected on the pituitary MRI. The patient received an open right adrenalectomy following complete preoperative treatment with alpha and beta blockers. A mixed corticomedullar tumor with no malignant alterations was identified by the histology.
Discussion and Conclusion
A tumor made of chromaffin cells known as a pheochromocytoma exhibits symptoms and signs of elevated sympathetic activity. A cortisol-producing adenoma is the most frequent cause of Cushing's syndrome, which manifests as hypertension, diabetes mellitus, central obesity, proximal muscle weakness, purple striae, bone fractures, and irregular menstruation in females. We describe a rare example of a combined corticomedullar tumor of the right adrenal gland that simultaneously secreted cortisol and medullary hormones.

Keywords: Pheochromocytoma, Cushing syndrome, Adrenal incidentaloma
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EP5

A case of Conn syndrome presenting as persistent post-partum hypertension

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Introduction
Conn's syndrome is a well-known cause of secondary hypertension; however, its association with pregnancy is rare. We discuss an interesting case of Conn syndrome presented with severe hypertension 8 weeks post-partum.
Case report
A 34-years-old lady, previously fit and well, presented with severe hypertension (blood pressure–189/115 mmHg) and hypokalaemia (K-2.5 mmol/l) at 8 weeks post-partum. Antenatal records indicated she was normotensive throughout her pregnancy and had an uneventful delivery. She did not have family history of hypertension. She was not on any prescribed or over the counter medications and denied liquorice sweet consumption. Her BMI was 26 kg/m^2 and had no clinical features of Cushing's syndrome. Serum potassium was consistently low (2.5 mmol/l). Repeated measurements of renin and aldosterone showed undetectable renin <5 mu/l and high aldosterone between 828–1224 pmol/l. 24-hour urinary free cortisol was normal at 126 nmol/24 hrs. (reference range <165 nmol/l). Overnight dexamethasone suppression test showed appropriately suppressed cortisol of 18 nmol/l. Urinary met adrenalines were normal. Confirmatory biochemical test was not done as screening tests were strongly positive and patient had persistent hypokalaemia. MRI scan of the adrenals showed a 13×9 mm fat containing left adrenal adenoma. Adrenal vein sampling performed after correcting serum potassium showed a clear left side lateralisation and contralateral suppression (aldosterone/cortisol ration on the left was 18.4 and on the right was 0.3 with lateralisation index >60). She was treated with Ramipril 7.5 mg, Spironolactone 100 mg and Sando-K- 2 tablets twice a day and listed for urgent left adrenalectomy. Her blood pressure and potassium were well controlled on these medications.
Discussion and learning points
Hyperaldosteronism in pregnancy is associated with adverse maternal and foetal outcomes and hypertension is likely to be worsened in this period. Our case highlights an exceptional clinical scenario where Conn's syndrome was likely masked during pregnancy with no evident physiological consequences on mother and foetus. Review of the literature suggests that increased progesterone during pregnancy in some people may mask the effects of hyperaldosteronism 1. Therefore, symptoms are evident in these people after the child birth and women may present with post-partum hypertension1. Clinicians should be aware of the possibility of Conn's syndrome as a cause of post-partum hypertension especially when it is associated with hypokalaemia.
Reference
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EP6

Cushing syndrome due to ACTH-secreting pheochromocytoma

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Introduction
Pheochromocytomas are neuroendocrine tumors derived from chromaffin cells which secrete catecholamines. Cushing syndrome due to ACTH-secreting pheochromocytomas is a rare condition and early recognition and treatment is important to decrease morbidity and mortality.Case presentation: We present the case of an 53 years-old man who arrived at the hospital for pain in the right scapula agravated in the last three months with iradiation in the right flanc, heart palpitations, headache and weight loss of 10 kilograms in the last 6 months.

General examination revealed an abdomen without signs of peritoneal irritation, painful in the right flanc, high blood pressure (232/165 mmHg) and tachycardia (128/bpm). Blood tests showed leukocytosis (20 600/mm^3), mild normocytic normochromic anemia with hemoglobine at 10.8 g/dl, hyperglycemia (225 mg/dl) and slightly elevated liver enzymes (ASAT = 94 UI/I, ALAT = 92 UI/I, GGT = 197 UI/I). The computed tomography revealed a large solid adrenal mass measuring 100 mm in the largest diameter with an important vascularization. The patient was trasferred to our department, where he underwent further biochemical testing to establish the functional status of the tumor. Blood tests showed high values for plasma normetanephrines (56.16 nmol/l), urinary normetanephrines (109.39 µmol/24 H), plasma cortisol (2 270 nmol/l), free urinary cortisol (161 nmol/24 H), plasma ACTH level at 22 pg/ml, normal values for 11-deoxycortisol, total testosterone, DHEAS and aldosterone-renin ratio and slightly elevated values for plasma metanephrines (0.54 nmol/l) and urinary metanephrines (2.54 µmol/24 H). Considering the 50 times higher values of plasma and urinary normetanephrines and 2 times higher values of plasma and urinary metanephrines, the diagnosis of pheochromocytoma was established which also associated a secretion of cortisol. A fluorodeoxyglucose-positron emission tomography was performed before the intervention to exclude possible secondary determinations, which revealed an uptake only at the level of the right adrenal tumor. The treatment with alfa and beta blockers was started and the patient was sent to the surgery department for the excision of the adrenal mass. Post intervention the cortisol and the catecholamine values returned to normal.

Conclusion

Considering the ACTH values higher than 20 pg/ml with very high cortisol values before the surgical intervention and the normalization of cortisolemia after the extirpation of the adrenal tumor, we have considered that it was a Cushing syndrome due to ACTH-secreting pheochromocytoma.

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EP7

Clinical symptoms, imaging and hormonal tests that suggest phaeochromocytoma in a patient with a solitary fibrous tumor incidentally discovered in the adrenal gland

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The solitary fibrous tumor is a rare spindle cell neoplasm, originally described in the pleural cavity. However, it can occur in other locations. SFTs that originate from the adrenal gland tissue are extremely rare. To date, only single cases have been described in the literature. We present a case of a 61-year-old Caucasian man with a SFT of the left adrenal gland. The patient was hospitalized in the internal medicine department due to paroxysmal hypertension (up to 190/100 mmHg) and an episode of syncope. An abdominal computed tomography scan was performed, in which a lobular, well-demarcated, 63×66×70 mm, intense post-contrast tumor was described in the left adrenal gland. The overall radiological picture was indicative of a pheochromocytoma. In hormonal tests, slightly elevated normetanephrine and 3-metoxytramine concentrations were found in 24-hour urine collection. Elevated hemoglobin, increased erythrocyte count, and elevated erythropoietin concentration were observed and the suspicion of polycythemia vera was raised. The patient required numerous bloodletting. Genetic tests did not show pathological variants in the *JAK2* gene. The patient was qualified to left adrenalectomy. Pathomorphological examination revealed a SFT with a diameter of 5.5 cm made of a network of interconnecting vessels of different caliber (immunohistochemically: CD31+, CD34+) focally with small visible atypia of endothelial cells, between which bright CD99+ cells were visible, and in part ERG+, bcl2-. The proliferative activity of Ki67 was about 10%. In postoperative follow-up tests 24-hour urinary fractionated metanephrines concentration and the blood count results have returned to normal ranges. The patient remains under regular surveillance. SFTs are usually indolent tumors that do not give certain clinical manifestations. They are extremely rare tumors, which may present with various uncharacteristic symptoms and should be considered in the differential diagnosis of an incidentally discovered adrenal mass.

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EP8

Metabolic changes in transgender people after gender-affirming hormone therapy

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Introduction

Demand for health care for transsexual people has increased exponentially in last years, especially among adolescents and young adults. Gender-affirming hormones (GAHs) are initiated to accommodate secondary sexual characteristics to the desired sex. Published studies about metabolic repercussion of GAHs are heterogeneous and report diverse results. Our objective is to evaluate the effect of GAHs on cardiovascular risk factors in transsexual population treated in our hospital.

Methods

We design a retrospective before-and-after study to evaluate changes in anthropometric parameters, blood chemistry analyses and metabolic comorbidities in transgender population treated with GAHs at least one year in Hospital Puerta del Mar between January 2017 and December 2020.

Results

A total of 227 transgender people were included in the study, 136 (59.91%) transmen and 97 (40.09%) transwomen. GAHs was initiated with median age of 18 (16–23) years old without significant differences between genders. It was detected a significant increase in weight, BMI and systolic and diastolic blood pressure, as well as a worse lipid profile in both genders. Likewise, prevalence of dyslipidemia and hypertension increased in transmen ($P<0.001$ and $P=0.004$, respectively) and transwomen ($P=0.035$ and $P=0.002$, respectively). Glycated hemoglobin increased significantly [32 (31-33) vs 33 (32-37) mmol/mol; $P=0.040$] in transmen and fasting blood glucose [4.66 (4.33-4.88) vs 4.77 (4.38-5.11); $P=0.008$] in transwomen, although it did not translate into a higher risk of prediabetes.

Conclusion

In our setting, there is a higher risk of dyslipidemia and hypertension and a tendency towards weight gain after one year of the THAG in transmen and transwomen. Prevalence of prediabetes did not increase and any new cases of type 2 diabetes mellitus were detected. No cardiovascular events or thromboembolic processes were reported during the study period.

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EP9

The role of early postoperative aldosterone in saline infusion test in the prediction of primary aldosteronism remission

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Objectives

This study aimed to assess the ability of aldosterone in saline infusion test (SIT) to predict biochemical remission of primary aldosteronism.

Methods

We retrospectively analysed 42 patients (19 (45%) females, mean age 49±12 years) with primary aldosteronism who underwent adrenalectomy (after adrenal vein sampling confirmation of unilateral disease) from 2017 to 2022. Aldosterone in SIT was determined on the fifth postoperative day, as well as 6-12 months after surgery, together with the aldosterone-to-renin ratio (ARR). Biochemical remission (complete, partial, or absent) of primary aldosteronism was defined according to the Primary Aldosteronism Surgical Outcomes (PASO) criteria.

Results

On the fifth postoperative day, 28 (66.7%) patients (group 1) had aldosterone in SIT <139 pmol/l, indicating complete biochemical remission; in 11 (26.2%) patients (group 2), aldosterone concentration in SIT was between 139 and 277 pmol/l which is consistent with partial biochemical remission; and 3 (7.1%) patients (group 3) had aldosterone in SIT >277 pmol/l, implicating absent biochemical remission. However, at the follow-up after 6-12 months, in four patients from group 1 ARR and aldosterone in SIT were consistent with partial biochemical remission. Similarly, in nine patients from group 2, and in two patients from group 3, ARR suggested complete biochemical remission. There was no statistically significant difference between these groups ($P=0.646$). Overall, 35 (83.3%) patients in our sample achieved complete biochemical remission, while 7 (16.7%) patients achieved partial biochemical remission.

Conclusions
Our results suggest that early postoperative aldosterone in SIT does not predict biochemical remission of primary aldosteronism.

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EP10

Hair cortisol measurement in the diagnosis and management of adrenal disorders

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Introduction
The acute status of the hypothalamic-pituitary-adrenocortical (HPA) axis is routinely assessed by the measurements of cortisol in blood, saliva, and urine. Because cortisol is continuously deposited in the growing hair shaft, hair cortisol can serve as a practical measure of long-term retrospective HPA axis activity. The purpose of this review is to present the relevance of hair cortisol measurement in the diagnosis and management of Cushing's syndrome and adrenal insufficiency.MethodsA systematic search of literature was conducted using the search terms hair cortisol, Cushing's syndrome, adrenal insufficiency, diagnosis, and management.
Results
Adult scalp hair grows at a rate of approximately 1 cm per month. A 1 cm of hair growth would represent total HPA axis activity of the previous 1 month. Therefore, the most proximal 1-cm hair cortisol is the best marker for the recent cortisol production. Longer hair samples can reflect cortisol production over months or years. For the measurement of hair cortisol, a 3-cm sample is taken from the posterior vertex of the scalp. If stored at room temperature and in intact hair, cortisol is stable for more than a year. Commercial kits (e.g., ELISA) can be used for the measurement of hair cortisol. The natural color of hair does not impact hair cortisol levels but excessive shampooing, hair dying, and prolonged exposure to UV light can diminish the cortisol levels. Obviously, baldness prevents the hair collection for cortisol measurement. Hair cortisol can be used as an initial or supportive diagnostic test for Cushing's syndrome with high sensitivity and specificity. The most proximal 1-cm hair cortisol is the best marker of hypercortisolemia. Hair cortisol measurement also helps assessing the natural history of hypercortisolism and adrenal insufficiency by estimating the duration of the disease before diagnosis. Hair cortisol levels may also be useful in the monitoring of disease progression and treatment efficacy of adrenal disorders. However, since hair cortisol levels are not sensitive to the circadian fluctuations of cortisol, they cannot replace blood and salivary cortisol measurements.
Conclusion
Hair cortisol measurement is a new non-invasive approach to assess long-term retrospective HPA axis activity when diagnosing adrenal disorders. The most proximal 1-cm hair cortisol is the best marker of hypercortisolemia and can be used as an initial diagnostic test for Cushing's syndrome. Hair cortisol is also useful in monitoring disease progression and treatment efficacy of adrenal disorders.

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EP11

Carriers of a pathological variant in CYP21A2 gene– clinical and hormonal status

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Introduction
21-hydroxylase deficiency (21OHD) is an autosomal recessive disorder and the diagnosis is confirmed by the presence of at least two biallelic pathogenic variants. The phenotype is determined by the less deleterious variant. The relevance of hormonal assessment to distinguish between heterozygote carriers of pathologic mutations and non-carriers or genetically defined 21OHD patients is still a matter of debate. Identifying the heterozygous genotype is important in adult life for a correct genetic counselling and a personalized approach of future pregnancies.
Materials and methods
We selected a group of Romanian paediatric patients with hyperandrogenism manifested as premature pubarche, accelerated growth, apocrine body odour, and seborrhoea in childhood ($n=19$) and hirsutism, oligomenorrhoea and acne in adolescence ($n=12$). 17OH-progesterone levels were measured by ELISA (reference values <2 ng/ml). MLPA and Sanger sequencing were used to establish CYP21A2 gene mutational status. All patients gave their informed consent for the study.
Results and discussion
After molecular analysis we identified 17 carriers of a pathologic variant in CYP21A2 gene (carrier-group) and 14 patients with genetic confirmation of 21OHD (21OHD-group). The pathologic variants identified in the carrier-group were V282L (35.71%), P31L (28.57%), P454S (21.43%), R92* (7.14%) and I173N (7.14%). We also identified 3 patients with heterozygous Q319* mutation but MLPA also revealed heterozygous duplication of CYP21A2 gene so we excluded them from the analysis. Patients included in 21OHD-group were homozygous or compound heterozygous for pathologic variants identified in the carrier-group and the diagnosis was non-classic or simple-virilizing form of 21OHD. 17OH-progesterone levels were significantly lower in carrier-group vs 21OHD-group (median 2.06 ng/ml vs 20 ng/ml). For the carrier-group the values are slightly increased or high-normal compared to kit reference values.
Conclusion
Clinically manifested hyperandrogenism with or without a concomitant increase of 17OH-progesterone could be a criterion for investigation of possible heterozygous carriers of a pathologic variant in CYP21A2 gene in paediatric population.

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EP12

Myocardial Infarction with non-obstructed coronaries: uncommon presentation of pheochromocytoma

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Background
Pheochromocytoma (PHEO) is a rare neuroendocrine tumour, classically presenting with hypertension, palpitations and headaches. Some patients have atypical presentations. We report a case of Myocardial Infarction with non-obstructed coronaries (MINOCA) as the key to unravel the diagnosis of PHEO.
Clinical case
A 53-year-old man with type 2 diabetes mellitus and hypertension (under gliclazide MR 60 mg id, bisoprolol 5 mg id, ramipril 5 mg id and atorvastatin 40 mg id), presented in the emergency room with nausea, vomiting, retrosternal crushing pain and palpitations. Over the past year he had frequent hyperadrenergic spells: excessive sweating, thoracic pain, headaches, tremor, pallor, sometimes accompanied by systolic blood pressure over 200 mmHg. Six months earlier, his echocardiogram showed left ventricular hypertrophy and his myocardial perfusion test (scintigraphy) showed abnormalities in the inferior-apical wall, but coronary angiography excluded obstructive coronary disease. CT scan chest revealed a 27 mm left adrenal nodule not typical of an adenoma. Clinical examination was unremarkable with a blood pressure of 107/68 mmHg.. His electrocardiogram showed sinus rhythm with T wave inversion in aVL and elevated troponins: 224 ng/l at baseline and 253 ng/l after 3 h (normal <14 ng/l). Bedside echocardiography was suggestive of stress cardiomyopathy. New coronary angiography showed normal coronary arteries. Patient was managed as MINOCA and underwent Cardiac MRI which revealed mild left ventricle hypertropohy and mild biventricular systolic dysfunction, but no signs of oedema or fibrosis. The clinical evolution was favourable, without symptomatic recurrence. Systolic dysfunction recovered and the patient was discharged (stopped beta-blocker). After discharge, he continued to have daily hyperadrenergic spells. Further investigation revealed raised urine metanephrine 569 µg/24h (<349), noradrenaline of 207 µg/24 h (<89), adrenaline 200 µg/24 h (<19), and plasma metanephrine 346.7 pg/ml (<89). Abdominal CT scan confirmed left adrenal nodule 3 cm compatible with PHEO. We slowly titrated doxazosin which managed to control the spells. MIBG scintigraphy revealed fixation on the left adrenal mass. The patient will undergo laparoscopic left adrenalectomy.
Discussion
This case illustrates the importance of thorough history taking and investigation for the underlying aetiology of an atypical chest pain. Even though the patient presented with

classical symptoms over a year, the diagnosis remained elusive. Cardiac complications are an uncommon presentation of PHEO. Early recognition of PHEO is crucial to improve clinical outcomes among these patients.

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EP13

Evaluating the diagnostic capacity of the saline infusion and captopril challengetests for primary aldosteronism

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Introduction
Primary aldosteronism (PA) is the most common cause of secondary hypertension. Guidelines recommend a confirmatory test in the majority of suspected cases: oral sodium loading, saline infusion test (SIT), captopril challenge test (CCT), or fludrocortisone suppression test. The SIT and CCT are most commonly used in clinical practice to study autonomous aldosterone secretion.
Objectives and Methods
We compared the CCT's diagnosis performance to that of the SIT. A retrospective study of PA confirmatory tests was conducted at Hospital Universitario La Paz (Madrid, Spain). Tests performed between 2019 and 2022 were included. All cases underwent confirmatory tests (CCT or SIT) according to the clinician's preference or the patient's characteristics and comorbidities. Antihypertensive medications were changed or discontinued for the confirmatory test following the guidelines. Dietary sodium intake was unrestricted. For CCT, patients received 50-mg captopril orally at 9 AM. The SIT involved the infusion of 2L of 0.9% saline IV over 4 hours. Both tests were performed in a seated position. The results of the different tests were compared.
Results
60 confirmatory tests were performed: 27 CCT and 33 SIT (Table 1). In comparison to CCT, the SIT got more indeterminate results (7.4% vs 39.4%, P 0.014). Age, gender, history of hypertension or hypokalemia, renin and aldosterone determinations (screening and during tests), urine aldosterone (if studied), presence of an adrenal nodule, or 1mg dexamethasone suppression test (if studied) did not differ between groups. Some patients with indeterminate results underwent a second confirmatory test. CCT was performed on 6 patients with non-conclusive SIT, with 5 definite results (2 positives and 3 negatives) and 1 indeterminate. On the other hand, the only patient who had an indeterminate CCT and underwent a SIT, also obtained an inconclusive result.
Conclusion
In diagnosing or ruling out PA, the CCT (50 mg) was more accurate than SIT. For the vast majority of patients with an indeterminate SIT, the CCT yielded a conclusive result.
Table 1

	Captopril Challenge Test (n=27)	Saline Infusion Test (n=33)
Indeterminate result	2	13
Positive result	14	13
Negative result	11	7

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EP14

Paraganglioma mimicking a tumor of the liver in an elderly patient

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Introduction
Paragangliomas are neuroendocrine tumors that are derived from the embryonic neural crest cells. Because the paraganglia are widespread through the body, paragangliomas can be found in unusual anatomic locations and the diagnosis can be hard to establish. Case presentationWe present the case of an 72 year-old, hypertensive woman who arrived at the hospital for pain in the right hypochondrium. General examination revealed an abdomen without signs of peritoneal irritation, high blood pressure (170/80 mmHg) and tachycardia (110/bpm). Blood tests showed minimum leukocytosis and slightly elevated liver enzymes. Routine abdominal ultrasound revealed a mass measuring 34/32 mm in the caudate lobe of the liver. Consequent computed tomography described a well-defined liver mass measuring 40/34 mm, adjacent to caudate lobe, para-aortic. The patient underwent endoscopic ultrasound-guided fine needle aspiration, without complications, to establish the tumor type. The histopatology examination revealed compact cell nests with vesicular nuclei, absent mitoses and amphophilic cytoplasm, without well defined boundaries. Imunohistochemical testing found negative results for keratins and positive staining for S-100 in sustentacular cells and positive results for cromogranin A and synaptopysin in chief cells, with a Ki 67 of 1-2%, being established the diagnosis of paraganglioma. The patient was trasferred to our department, where she underwent further biochemical testing to establish the functional status of the tumor. Blood tests showed high values of plasma normetanephrines (1127.99 ng/l), slightly elevated values for metanephrines (124.92 ng/l) and normal values for methoxytyramine. Chromogranin A couldn't be measured because the patient was receiving proton pump inhibitors. After establishing the diagnosis of secretory paraganglioma, the patient started the treatment with alfa and beta blockers and was sent to a surgery department.ConclusionThe reported case is interesting because of the age of the patient and the way the diagnosis was established. Most paragangliomas are diagnosed in younger people, mostly in their third to fifth decade. Even if the majority of sympathetic paragangliomas are located in the abdomen, given the rarity of the tumor, the diagnosis can be missed without a degree of suspicion and further investigations. In our case the diagnosis was established after biopsy, which is **contraindicated** in a patient suspected of having paraganglioma because of the associated risks like severe hypertension, hemorrhage or fibrosis at the intervention site and because the aspirates can be difficult to distinguish from other neoplasms.

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EP15

A single center experience of extraadrenal paragangliomas–clinical and molecular analysis

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Paragangliomas are rare neuroendocrine neoplasms that arise from chromaffin tissue commonly located in the adrenal medulla, pre-aortic and paravertebral sympathetic plexus or skull base. About 30% of paragangliomas have a genetic basis. They may be associated with autosomal dominant inheritance of variants in the gene encoding succinate dehydrogenase or may coexist in genetically determined endocrine syndromes. The study aim was to analyse clinical and molecular data of patients with extraadrenal paraganglioma from one clinical center in 2016-2021.
Materials and Methods
In all paraganglioma patients (29 cases), the age of diagnosis, clinical symptoms, location, 24-hour urinary fractionated metanephrines concentration, serum concentration of chromogranin A, the largest dimension of the lesion, and distant metastases were evaluated. Molecular analysis for pathogenic variants in *SDHB*, *SDHC*, *SDHD*, *RET*, *MEN1*, *MAX*, and *VHL* genes was performed using next-generation sequencing methods.
Results
22 women and 7 men were enrolled. Patients were divided into four subgroups according to location, head and neck - 7 patients, thorax - 3 patients, abdomen - 15 patients, and pelvis - 4 patients. The median age of diagnosis for each group was: head and neck 62 years (range 43 - 70), chest 45 years (range 34 - 52), abdomen 58 years (range 18 - 73), pelvis 45.5 years (range 20 - 72). The most common symptom was hypertension, affecting 93.1% of the patients. Tachycardia was present in 27.6% of the study group. The study showed the highest urinary fractionated normetanephrine concentration in patients with paragangliomas with pelvic location (P=0.016)–median 6134.1 µg/24 h (range 1053.8 - 12650.9) [ref. range 88.0 - 440.0]. There was no significant difference in serum concentration of chromogranin A between groups. Molecular alterations within the genes analysed were found in 5 patients: 3 pathogenic variants within the *SDHD* gene were identified, 1 variant of uncertain significance (VUS) in *SDHD* and 1 VUS in *SDHB*, respectively. Molecular alterations were observed in 71.4% of patients with paragangliomas with head and neck localization and were not identified at

other locations. Distant metastases were found in 14.3% of the patients in paragangliomas of the head and neck region, 33.3% of the thorax, 6.7% of the abdomen, and 25.0% of the pelvis.
Conclusions
The pelvic location of the paraganglioma was associated with a statistically higher urinary fractionated normetanephrine concentration. Pathogenic variants within the genes analysed found in the study group involved patients with localization in the head and neck region.

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EP16

Adrenal venous sampling in tertiary centre from 2015. to 2022

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Background
Adrenal venous sampling (AVS) is considered the gold standard for differentiating an aldosterone- producing adenoma (aPA) from bilateral adrenal hyperplasia (BAH)
Objective
The aim of this study is to present our experience with this method in our hospital.
Methods
We performed a retrospective analysis of 105 patients who underwent the AVS protocol at our centre between 2015 and 2022 for PA.
Results
AVS was performed 115 times in 105 patients, and in 20 patients AVS was performed 2 times. AVS was successful in 86 patients (82%). Among them, 66 patients were female (63%) and median age of all our patients was 53 years (20-75). In 62 patients (65%), the potassium level was lower than 3.6 mmol/l. The main reason for work-up was arterial hypertension in 42 patients (40%). AVS result and CT scan were compatible in 59 patients (60%). According to AVS, APA was diagnosed in 58 (55%) patients, BAH in 37 (35%) patients and in 10 (10%) patients the diagnosis was inocclusive. Surgery was performed in 46 (44%) patients and 58 (56%) patients were treated with medication. Complete biochemical remission was seen in 20 (84%) patients and partial biochemical remission in 2 (8%) patients. 2 (8%) patients had subclinical Cushing's syndrome and did not show biochemical remission. Complete clinical remission was seen in 13 (38%) patients, partial clinical remission in 18 (53%) and 3 (9%) patients had no clinical remission. AVS was more successful in the last 4 years than in the years before (83% vs 69%).
Conclusion
Our results show a high rate of successfully performed AVS. Prolonged hypertension could be one of the reasons for partial biochemical remission.

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EP17

Adrenal lesions in patients with familial adenomatous polyposis

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Introduction
Familial Adenomatous Polyposis (FAP) is an autosomal dominant disease classically characterized by the development of hundreds or thousands of adenomas in the rectum and colon during the second decade of life. Almost all patients will develop colorectal cancer (CRC) if not identified and treated at an early stage. It is a multisystem growth disorder so there is an increased risk of developing extraintestinal manifestations. In this context, an increase in adrenal pathology compared to the general population has been described. We aimed to report the frequency, functional characteristics and progressions of adrenal lesions in FAP patients.
Materials and Methods
Prospective study, selecting 17 living patients diagnosed and registered with APC mutations under follow-up from the Digestive Department of the Hospital Universitario de Navarra (HUN) with current or past follow-up in the Endocrinology Department. Radiological tests, clinical, and analytical variables were analyzed.
Results
The study population included 12 men (64.7%) and 5 women (35.3%), with a mean age of 47 years. The median age at diagnosis of FAP was 28 years, with a mean follow-up time of 16 years. All patients had an abdominal imaging study (CT or MRI), detecting lesions in 5/17 (31.25%). All were incidental findings presented as non-functioning adenomas in the analytical tests performed. The study consisted of the overnight 1mg dexamethasone suppression test, catecholamine/metanephrine determination, adrenal androgen production, and if appropriate, screening of primary hyperaldosteronism. None showed significant growth during follow-up (defined as changes in the size of ≥ 2 mm were considered clinically significant). No major endocrinological alterations (defined as nodular disease or thyroid carcinoma, thyroid autoimmunity, diabetes, obesity) were detected when comparing both groups. There were also no differences in gender, age or time since diagnosis.
Conclusion
Adrenal lesions are common in patients with FAP who undergo abdominal imaging. They appear to follow a benign and slowly progressive course, presenting clinically and analytically as non-functioning lesions.

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EP18

Insulin Signaling in Hyperactivation of the HPA Axis in Metabolic Diseases

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Stress can lead to an increase in body fat and obesity as main clinical conditions preceding the metabolic syndrome. In metabolic stress, hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis has been observed, resulting in increased steroidogenesis and alteration of cortisol secretion[1]. This increased sensitivity of the HPA axis may be related to the development of comorbidities or severe illness in patients with metabolic diseases and *vice versa*. Disorders of the HPA axis, e.g., Cushing's disease, resulting from overproduction of ACTH, share similar clinical symptoms with metabolic diseases. The molecular signaling mechanisms that cause such changes in the HPA axis under metabolic stress remain elusive. Previous studies indicate a role of insulin in the regulation of adrenal steroidogenesis by upregulating the transcriptional activity of NR5A1[2]. Here, we study the molecular mechanisms to insulin-induced hyperactivation of the HPA axis and characterize the molecular changes that lead to altered cortisol secretion. We generated non-adherent spheroids from primary adrenocortical cells *in vitro* and treated these with insulin. This resulted in an increase of spheroid diameter over time compared to control, indicating greater cell expansion following insulin treatment. Similarly, repeating this experiment with adherent primary anterior pituitary stem cell colonies, we observed an increase in colony size when treated with insulin compared to control. This indicates that the stem cell populations of the adrenal and pituitary gland are responsive to insulin stimulation, likely leading to increased proliferation. This is complementary to our previous studies where we revealed increased secretion of aldosterone in insulin-stimulated adrenocortical cultures[3]. To identify signaling pathways related to insulin stimulation, we performed bulk RNA sequencing of *in vitro* primary cultures of adrenocortical and pituitary cells with and without insulin treatment. Analysis of these data sets reveals specific signaling pathways that are candidates in regulation of metabolic stress *in vivo*. Using mouse models of obesity and diabetes along with genetic lineage-tracing studies, we aim to decipher the role of these pathways on HPA axis stem/progenitor cells during metabolic stress. The outcomes will pave the way for a better understanding of HPA axis activity during metabolic stress adaptation, and the role of the HPA axis in patients suffering from metabolic diseases.
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EP19

21-hydroxylase deficient congenital adrenal hyperplasia in adult endocrinology clinics of turkey: A nationwide multicenter study

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Introduction
Congenital adrenal hyperplasia (CAH) is a group of autosomal recessively inherited disorders that are characterised by inactivating mutations at various steps of adrenal steroidogenic pathways causing defective cortisol biosynthesis. 21-Hydroxylase enzyme deficiency (21-OHd) constitutes more than 95% of all CAH cases.
Material & Methods
Medical records of patients with all forms of CAH from 19 adult endocrinology clinics located at six different geographical regions of Turkey are evaluated in this multicentre study. Findings of 21-OHd CAH cases ($n=181$) eligible for analysis are given.
Findings
There were 101 (55.8%) classical and 80 (44.2%) nonclassical 21-OHd CAH cases. General features of cases can be found in Table. More patients in nonclassical CAH group were married and had children. Reconstructive genital surgery was performed in 54 (78.3%) of classical CAH females and 42 (77.8%) of them had no children. Data about genetic analysis were reached in 120 cases (57 classical CAH, 63 NCAH). V281L mutation was detected in 21 (33.3%) of 21-OHd NCAH patients.
Discussion
Interpretation of findings of this study will improve our knowledge about CAH and will inevitably result in better health service.

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21-OHd CAH ($n=181$)	Classical CAH ($n=101$) (55.8%)	Non-Classical CAH ($n=80$) (44.2%)	*P*
Gender (*n*, %)			
Male	31 (30.7)	8 (10)	0.002
Female	69(68.3)	72 (90)	
Female to male	1 (1.0)		
Age at diagnosis (years)	4.99 ±9.86	20.02 ± 12.67	0.02
Time on follow-up (years)	17.49±9.43 ($n=97$)	7.23±8.71 ($n=71$)	0.176
Education Level (*n*,%)			
Unknown	17 (16.8)	12 (15)	0.375
Preliminary School and below	10 (10)	10 (12.6)	
High School	46 (45.5)	30 (37.5)	
University degree and above	28 (27.7)	28 (35.1)	
Diagnosing Physician ($n=180$) (*n*,%)			
General or Pediatric Endocrinologist	83 (82.2)	20 (25.3)	0.000
Internal Medicine Specialist/ Adult Endocrinologist	8 (7.9)	54 (68.4)	
Gynecologist or Others	10 (9.9)	5 (6.3)	
Consanguinity between parents (*n*, %)			
YES	54 (53.5)	14 (17.5)	0.000
NO	36 (35.6)	42 (52.5)	
Unknown	11 (10.9)	24 (30)	
Marital Status (*n*, %)			
Single	65 (64.4)	41 (51.2)	0.003
Married	21 (20.8)	33 (41.3)	
Divorced	0 (0.0)	2 (2.5)	
Unknown	15 (14.9)	4 (5.0)	
Having children (*n*, %)			
YES	6 (5.9)	29 (36.3)	0.000
NO	77 (76.2)	40 (50.0)	
Unknown	18 (17.8)	11 (13.8)	
Used Glucocorticoid name(*n*, %)	($n=101$)	($n=77$)	
Dexamethasone	21 (20.8)	8 (10.4)	0.000
Methylprednisolone	5 (5.0)	0 (0.0)	
Prednisolone	23 (22.8)	9 (11.7)	
Hydrocortisone	43 (42.6)	12 (15.6)	
Dexamethasone + Methylprednisolone	1 (1.0)	0 (0.0)	
Dexamethasone + Hydrocortisone	3 (3.0)	0 (0.0)	
Unknown-None	5 (5.0)	48 (62.3)	

EP20

Increased sclerostin concentration in patients with primary adrenal insufficiency

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Background
Sclerostin is a protein secreted by osteocytes, that inhibits Wnt/ βcatenin signaling and was suggested to play a role in glucocorticoid-induced osteoporosis in mice. In humans data are inconsistent. Patients with primary adrenal insufficiency need lifelong replacement therapy with glucocorticoids and mineralocorticoids, which may influence their bone quality.
Aim
The aim of the study was to evaluate sclerostin concentrations, densitometry parameters, and trabecular bone score in patients with primary adrenal insufficiency in comparison to control group.
Materials and Methods
We included 29 patients (62% females) with diagnose of autoimmune primary adrenal insufficiency (mean age 49.7±11.7 years, mean duration of the disease 13.2± 13.6 years) and 33 healthy subjects (adjusted with age, sex and body mass index). Bone mineral density at the femoral neck, lumbar spine, total body and

trabecular bone score were evaluated. Serum sclerostin concentrations were measured.
Results
Mean serum sclerostin concentration was significantly higher in patients with adrenal insufficiency than in control group (44.7±23.5 vs 30.7±10.4 pmol/l, $P=0.006$). There were no significant differences in densitometry parameters (Tscore, Z-score, bone mineral density) and trabecular bone score in patients with adrenal insufficiency and control group. There was a negative correlation between trabecular bone score and the duration of adrenal insufficiency and age, also a negative correlation between femoral neck and total densitometry parameters and 24-hour urine cortisol. Sclerostin concentration correlated positively only with free thyroxine concentration ($R=0.486$, $P=0.009$; no significant correlation with serum TSH), there were no significant correlations with any other clinical or biochemical parameters.
Conclusions
The sclerostin concentration was higher in patients with primary adrenal insufficiency in comparison to control group. This finding needs further studies.

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EP21

Aldosterone/direct renin ratio (ADRR) in the screening of patients with primary aldosteronism

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Background
Primary aldosteronism (PA) is the most common endocrine cause of secondary hypertension. It occurs in 5%-10% of hypertensive patients. PA is a group of disorders associated with semi-autonomous hypersecretion of aldosterone. Laboratory diagnosis in patients with suspected PA consists of screening tests aimed at determination of serum/plasma aldosterone concentration, direct renin concentration (DRC) and calculation of the aldosterone/direct renin ratio (ADRR). The aim of the study was to assess the usefulness of aldosterone and direct renin concentrations using the immunochemiluminescent method (CLIA, LIAISON XL® analyzer, DiaSorin, Italy) and to use the ADRR ratio as a screening test in the biochemical diagnosis of patients with suspected primary aldosteronism.
Methods
Patients were divided into 2 groups: 1. Patients with primary aldosteronism ($n=35$) 2. Patients with adenoma + hypertension ($n=200$) Serum aldosterone concentration, direct plasma renin concentration and aldosterone/DRC ratio (ADRR ratio) were determined in all patients. Aldosterone and direct renin concentrations were determined by immunochemiluminescent assay (CLIA) on a LIAISON XL® analyzer (DiaSorin, Italy). The ADRR is shown as ng/dl/μIU/ml.
Results
Serum aldosterone levels in patients with PA ranged from 9.92 to 100 ng/dl. Aldosterone levels were <10 ng/dl in 2 patients, between 10-15 ng/dl in 6 patients, and >15 ng/dl in 27 patients. The optimal cut-off for aldosterone was 13.8 ng/dl (AUC 0.8816; $P<0.0001$). Sensitivity and specificity for serum aldosterone concentration for patients with PA were 79% and 82%, respectively. DRC in patients with PA was in the range of 0.5–10.1 μIU/ml. The optimal cut-off for DRC in patients with PA was 4.22 μIU/ml (AUC 0.9466; $P<0.0001$). Sensitivity and specificity for DRC were 83% and 94%, respectively. The aldosterone/renin ratio (ADRR) was calculated from the aldosterone concentration and DRC. The optimal cut-off point discriminating PA patients from adenoma hypertensive patients was 3.85 ng/dl/μIU/ml (AUC 0.9843; $P<0.0001$), achieving 94% sensitivity and specificity.
Conclusion
Determination of aldosterone and renin levels using the CLIA method and the use of the ADRR ratio show a high diagnostic value as a screening test for patients with PA.

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EP22

Clinical presentation and cardivascular events in primary hiperaldosteronism

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Introduction
Primary aldosteronism (PA) is characterized by symptoms caused by hypertension and hypokalemia. Some cardiovascular events are found to be more common due to the additional negative effect of aldosterone. The aim of the study was to analyse clinical characteristics of the PA due to adenoma (APA) and to compare the frequency of cardiovascular diseases with those found in adrenal Cushing' syndrome (CS) and adrenal adenoma associated with essential hypertension (A+HT). Material and method: The study group of PA included 40 patients (25 females, 15 males). The study groups (CS $n=20$; A+HT $n=40$) did not differ by age and sex.
Results
The mean systolic and diastolic arterial pressures were significantly higher in PA group than A+HT group ($P=0.004$; $P=0.002$; respectively) and all had hypokalaemia. PA was more common in younger women (20-40 years 24% vs 6.7%) and older men (>60 years 8% vs 60%). The most common symptoms of PA were evenly distributed: muscle weakness, pain, cramps, tingling (45%), headache, brain fog (32.5%) and fatigue (20%). Patients younger than 50 years suffered from muscle paresis (10%) and EPH-gestosis (7.5%). Only patients older than 50 years suffered from cardiovascular complications: atrial fibrillation 15%, cerebrovascular insult 3%, myocardial infarction 7.5%, angina pectoris 6%, chronic heart failure 7.5%, and aortic aneurysm 5%. Chronic renal failure was found in 20% of patients. There were no significant differences in the presence of cardiovascular and cerebrovascular events between groups.
Conclusion
We found a higher tendency for cardiovascular, renal and cerebrovascular events in PA that was not significant.

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EP23

REPLACE: Effect of hydrocortisone and placebo in patients with partial adrenal insufficiency after cessation of glucocorticoid treatment; A study protocol for a multi-centre, randomised, double-blinded, placebo-controlled clinical trial

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Background
Glucocorticoid (GC) formulations are widely used as anti-inflammatory treatment, and synthetic GC, e.g. prednisolone, is the cornerstone treatment of polymyalgia rheumatic (PMR) and giant cell arteritis (GCA). Long-term pharmacological GC treatment may induce adrenal insufficiency (GIA). Adrenal function is, however, not routinely assessed after discontinuation of long-term GC treatment, and it is unknown, if hydrocortisone replacement is beneficial. This study aims to generate evidence-based guidance for the management of GIA due to long-term GC treatment.
Methods
The REPLACE study is a multi-centre, randomised, double-blinded, placebo controlled 1-year study. Participants are patients diagnosed with PMR and/or GCA, who have been in GC free remission for 2-12 weeks after long-term prednisolone treatment. Eligible patients undergo an ACTH test, and group assignment depends on the cortisol response: In both RCT and control groups a fasting, standardized baseline visit includes patient reported outcome (PRO), physical and psychological health. Patients in the RCT are randomized to either hydrocortisone or placebo for 1 year with repetition of baseline investigations at 6 and 12 months.
Outcomes
Primary outcome: Health related quality of life associated with adrenal insufficiency assessed by the Addison's disease-specific quality-of-life questionnaire (AddiQol-30).
Secondary outcomes: Using a study smartphone application (app), participant-reported information about intercurrent illness or stress, and symptoms attributable to adrenal insufficiency, are reported daily. Furthermore, ecological momentary assessments of the Multidimensional Fatigue Inventory, General Fatigue scale, are reported in the app in both stressed and unstressed conditions.

Exploratory outcomes: Additional questionnaire-based HRQoL (CushingQoL, SF-36v2, Single item Sleep Quality Scale and the International Physical Activity Questionnaire-S7S); incidence of adrenal crisis; cardiovascular health (blood pressure, arterial stiffness and coagulation markers); body composition and muscle function (DXA scan and physical tests); bone and calcium metabolism; glucose homeostasis; possibly normalization of adrenal function; and biomarkers of GC sensitivity and action.

Ethics and dissemination

The REPLACE study is in accordance with the Declaration of Helsinki; registered at EudraCT (2020-006121-65) and publications will be according to the International Committee of Medical Journal Editors recommendations.

Funding

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Status: Recruiting.

RCT-group	Cortisol level >100 nmol/l and <420 nmol/l	$n=150$
Partial adrenal insufficiency		
Control group 1	Cortisol level <100 nmol/l	$n=20$
Adrenal insufficiency		
Control group 2	Cortisol level >420 nmol/l	$n=60$
Normal adrenal function		

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EP24

Addison's disease with preserved glucocorticoid function in the Type 1 diabetes population: a diagnosis not to miss during routine diabetes follow-up

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Background

Prevalence of Addison's disease (AD) among patients with Type 1 diabetes mellitus (T1DM) is estimated at 0.2%, whilst prevalence of T1DM among patients with AD can be up to 14%. Residual adrenal function in patients with established AD may be present in up to 30% of cases but its clinical significance is not fully clear.

Aims

To evaluate the prevalence of AD with preserved glucocorticoid function in patients with T1DM at Newcastle Diabetes Centre. To describe the demographics, clinical presentation and investigations that led to the diagnosis of AD with preserved glucocorticoid function in these patients.

Methods

Review of electronic records for patients with T1DM registered at our centre and diagnosed with AD and/or prescribed steroids and fludrocortisone regularly.

Results

12 out of 2704 patients had a diagnosis of AD. The prevalence of AD in our T1DM population is 0.6%. 3/12 (25%) patients with AD demonstrated preserved or relatively preserved glucocorticoid function. All 3 patients had chronic, intermittent hyponatraemia with hyperkalaemia. Random cortisol level in 2 patients were 205 nmol/l and 479 nmol/l while the third patient was established on longterm immunosuppressant steroid therapy. The latter achieved a peak cortisol of 179 mmol/l on Short Synacthen Testing, suggesting preserved glucocorticoid function. None of the patients reported weight loss but fatigue was a commonly reported symptom.

Conclusions

AD with preserved glucocorticoid function, albeit a rare entity, is most likely to be encountered during routine follow-up in the T1DM clinic in patients with intermittent hyponatraemia or hyperkalaemia. Clinicians should be alert to investigate for AD in these patients. A random cortisol measurement may miss AD with preserved glucocorticoid function. In selected cases, clinicians should consider checking transtubular potassium gradients, serum bicarbonate, renin, aldosterone and ACTH levels, if short Synacthen test results are normal.

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EP25

Endocannabinoids in patients with adrenal incidentalomas. A new prognostic biomarker?

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Background

The majority of adrenal incidentalomas (AIs) are benign non-functioning adrenocortical adenomas (NFAIs), yet not clinically silent. Possible autonomous cortisol secretion (PACS) can also be diagnosed in up to 50% of patients. Endocannabinoids (ECs) have recently been studied regarding their role in the hypothalamo-pituitary-adrenocortical (HPA) axis; however, data are scarce in humans.

Aim

We aimed to assess hair EC [anandamide (AEA) and 2-arachidonoylglycerol (2-AG)] levels in patients with AIs compared to controls and their association with the hormone profile of these patients.

Methods

Forty-four patients diagnosed with AIs (32 NFAIs and 12 PACS) and 44 controls (without AIs in computerized tomography), referred to the Endocrinology Unit of the 1st Department of Internal Medicine of Laikon Hospital between June 2020 and July 2021, were recruited. Patients with serum cortisol (F) levels between 1.8 and 5 μg/dl post 1mg dexamethasone suppression test (1mg-DST) were classified in PACS group, whereas those with F levels < 1.8 μg/dl in NFAI group. Basal (8:00 am) F, adrenocorticotropic hormone (ACTH), dehydroepiandrosterone sulfate (DHEA-S) as well as 24-h urinary free cortisol (UFC) were also analysed. Hair samples were collected according to Society of Hair Testing guidelines and EC levels were measured by liquid chromatography tandem-mass spectrometry. Statistical analysis was conducted using SPSS version 28.

Results

The age, sex and body mass index as well as the prevalence of hypertension, dyslipidemia, diabetes mellitus type 2 and bone disease did not differ significantly between the groups. Significantly decreased hair AEA and 2-AG levels were found in patients with AIs compared to controls ($P<0.001$ and $P=0.002$ respectively) as well as between NFAI or PACS and controls ($P<0.001$ or $P=0.002$ and $P=0.038$ or $P=0.02$ respectively). Among the AI patients, EC levels were found lower in PACS group compared to NFAI, although not statistically significantly. AEA hair levels were negatively correlated with F levels post 1 mg-DST ($r_s=-0.257$, $P=0.033$), but not with F, ACTH, UFC or DHEA-S levels.

Conclusion

Data regarding the interaction between glucocorticoids (GCs) and ECs are scarce, contradictory and analysed mainly in animal models. In humans it seems that the chronic exposure to GCs has an inhibitory effect on the circulating EC levels. Our data showed that patients with AIs presented lower EC levels compared to controls enhancing the hypothesis of the suppressive effect of chronic hypercortisolism on hair EC levels. The role of ECs on HPA axis merits a more thorough analysis in larger human studies.

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EP26

Optimal application of captopril challenge test in the diagnosis of primary aldosteronism

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Objective

To evaluate the optimal parameters and the cut-off points of captopril challenge test (CCT) in the diagnosis of primary aldosteronism (PA) using chemiluminescence immunoassays (CLIA).

Methods

Patients with clinically suspected PA who admitted to our hospital between July 2021 and December 2021 were recruited. Both supine and upright aldosterone to renin ratio (ARR) were calculated in all the participants and 21 healthy volunteers. CCT was performed in all those ARR ≥ 25 and the first two out of three ARR < 25. Blood samples were drawn before, 1 h and 2 h after oral 50mg captopril for the measurements of plasma renin concentration (PRC) and plasma aldosterone concentration (PAC). PRC was measured by CLIA while PAC was measured by both CLIA and liquid chromatography-mass spectrometric (LC-MS/MS). ARR before CCT, at 1 h post-CCT and 2 h post-CCT were calculated. The suppression percentage of PAC and increasing percentage of PRC were also calculated. PA was established according to criteria. Informed written consent was obtained from all participants. This study was registered in chictr.org.cn (identifier, ChiCTR2100047984).

Results
Blood samples of 112 suspected PA patients and 21 healthy volunteers were collected to measure PAC using both CLIA and LC-MS/MS. A positive correlation ($r=0.804$, $P<0.001$) was observed between the two assays. CCT were performed in 45 with ARR $\geq$ 25 and 43 with ARR $<$ 25. Data were analyzed in 43 confirmed PA patients and 45 essential hypertension patients. Compare to the PAC, suppression percentage of PAC and increasing percentage of PRC, ARR at 2 h post-CCT presented the largest area under the receiver operating characteristic curve either PAC was measured by LC-MS/MS or by CLIA. The optimal CLIA-specific cut-off of 2 h post-CCT ARR was 26.0, with a sensitivity and specificity of 95.3% and 93.3%, respectively. Moreover, the specificity achieved to 97.8% when combining 2 h post-CCT ARR $>$ 26.0 with 2 h post-CCT PAC $>$ 15.000 ng/dl.
Conclusion
CLIA presents well correlation with LC-MS/MS in PAC measurement. 2 h post-CCT ARR is the most efficient parameter in PA diagnosis using CCT. The optimal cut-off point for 2 h post-CCT ARR is $>$ 26.0 in our study. The diagnosis is more specific when combining 2 h post-CCT ARR $>$ 26.0 with 2 h post-CCT PAC $>$ 15.000 ng/dl.

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EP27

Metanephrines work-up in patients diagnosed with incindentaloma - the influence of commonly used drugs on results interpretation

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Introduction
Due to the frequent occurrence of adrenal incidentalomas, diagnosis of their hormonal activity is a significant clinical concern. Approximately 7-10% of adrenal tumors are pheochromocytomas, which even in silent form can lead to hemodynamic instability during surgery. According to the ESE and ENSAT guidelines in any case of adrenal tumors greater than 1 cm pheochromocytoma should be excluded based on plasma metanephrines level and urinary metanephrines excretion. Such approach can be challenging in patients with significant comorbidities or when patients are on drug which interfere with analytical measurement.
Aim of the study
The aim of this study was to evaluate the effect of selected drug on metanephrines excretion in urine in patients with incidentaloma.
Materials
1,102 patients with incidentalomas confirmed by CT or MR were included in the study. Patients with a clinical or biochemical diagnosis of Cushing's or Conn syndrome as well as patients very likely having pheochromocytoma were excluded. In all patients, 24-hour urinary excretion of normetanephrine, metanephrine and 3-methoxytyramine were measured by high performance liquid chromatography (HPLC) with electrochemical detection. The information on concomitant medication (β-blockers, Ca-blockers, loop diuretics, thiazide diuretics, potassium-sparing diuretics, α-blockers, ACE inhibitors/aniotensin II receptor antagonists, metformin, other antidiabetic drugs, lipid lowering drugs, proton pump inhibitors, levothyroxines, thyreostatics, antidepressants, neuroleptics, benzodiazepines, glucocorticosteroids, B receptor agonists and M-receptor antagonists) from each patient were collected.
Results
The analysis showed that urine excretion of normetanephrine was significantly higher in patients (without medication vs medication) using β-blockers (288.9 vs 332.3 μg/24 h, $P<0.0001$), Ca-blockers (282.6 vs 333.8 μg/24 h, $P<0.0001$), loop diuretics (299.4 vs 374.5 μg/24 h, $P<0.0001$), α-blockers (299.3 vs 352.7 μg/24 h, $P=0.0001$), non-metformin antidiabetic drugs (301.0 vs 366.15 μg/24 h, $P=0.0001$) and neuroleptics (305.4 vs 384.3 μg/24 h, $P=0.0307$). Urinary metanephrine excretion was higher in patients taking α-blockers (109.2 vs 136,9 μg/24 h, $P<0.0001$) and was lower in patients taking non-metformin antidiabetic drugs (114.3 vs 99.3 μg/24 h, $P=0.0247$), antidepressants (114.3 vs 97.7=8 μg/24 h, $P=0.0207$) and glucocorticosteroids (114.6 vs 94.8 μg/24 h, $P=0.0043$) . Urinary 3-methoxytyramine concentration was higher in patients taking thiazide diuretics (191.8 vs 264.5 μg/24 h, $P=0.0031$), antidepressants (195.2 vs 317.9 μg/24 h, $P=0.0005$) and M-receptor antagonists (198.3 vs 284.6 μg/24 h, $P=0.0292$). The other drugs had no significant effect on the results of urinary excretion of catecholamines.
Conclusion
Many of the commonly used drug groups significantly affect the results of 24-hour urine collection of fractionated methanephrines. Interpretation of these results should be adjusted and take into account the effect of the drug groups used on the results obtained and individualized in the clinical context.

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EP28

Novel high resolution mass spectrometry profiling of free cortisol, cortisone, 6β- and 18-hydroxycortisol for the evaluation of glucocorticoid and mineralocorticoid disorders

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Introduction
Urine free cortisol measurements are routinely performed to evaluate hypercortisolism. Despite their analytical inaccuracy, immunoassay-based methods are frequently used. Advances in liquid chromatography high resolution mass spectrometry (LC-HRMS) facilitate the incorporation of powerful diagnostic tools into clinical laboratories with high analytical specificity that also allow simultaneous quantification of different metabolites and untargeted compound identification, which may be helpful to identify other clinically relevant metabolites or drugs.
Objectives
The aim was to validate a simple routine LC–HRMS method to quantify simultaneously cortisol, cortisone, 6β-hydroxycortisol, and 18-hydroxycortisol in human urine. In addition to the key role of urine cortisol measurements in Cushing's syndrome, the cortisol/cortisone ratio (11βHSD2 activity) is a sensitive marker for the apparent mineralocorticoid excess syndrome, the 6β-hydroxycortisol/cortisol ratio is a marker for CYP3A activity, and 18-hydroxycortisol levels are useful in the evaluation of primary hyperaldosteronism, especially familial forms.
Methods
Urine extraction was liquid-liquid with dichloromethane, chromatographic separation was performed by micro-LC and detection used accurate masses of steroids and simultaneous high resolution full scan acquisition. Validation included the assessment of linearity, matrix effect, accuracy, imprecision, selectivity, carry-over and comparison with a GC-MS method. We also quantified the 24-h urine excretion of the four steroids by LC-HRMS in 60 samples of patients with clinical suspicion or follow-up for hypercortisolism. The cross-reactivity of the measured steroids with commercial cortisol immunoassays (Liaison and Atellica) was also investigated.
Results
The analytical method was free of matrix effect and presented acceptable analytical performance. Cortisol concentrations in the urine of patients significantly correlated with cortisone and 6β-hydroxycortisol but not with 18-hydroxycortisol. Patients with antisteroidogenic drugs presented reduced CYP3A4 activity as assessed by the 6β-hydroxycortisol/cortisol ratio. The urines of patients without antisteroidogenic drugs ($n=41$), metyrapone ($n=12$), ketoconazole ($n=4$) and osilodrostat ($n=3$) presented, respectively, 6β-hydroxycortisol/cortisol ratios of 4.1 ± 0.5, 2.2 ± 0.5, 1.5 ± 0.6 and 0.1 ± 0.1 ($P<0.05$). In contrast, no differences were observed between these groups in the 11β-HSD2 activity calculated as the ratio cortisol/cortisone. Finally, cross-reactivity with 6β-hydroxycortisol and cortisone was demonstrated in cortisol immunoassays, which presented significantly higher urine cortisol results in comparison with LC-HRMS.
Conclusion
A rapid and accurate routine LC-HRMS method was validated, which is useful for routine evaluation of hypercortisolism and other disorders of glucocorticoid and mineralocorticoid metabolism. Cross-reactivity with 6β-hydroxycortisol may impact cortisol immunoassay reliability to monitor hypercortisolism medical therapies.

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EP29

A new LC-MS/MS method for simultaneous determination of six steroids in urine for the diagnostic workup of primary aldosteronism

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Background
The diagnostic workup of primary aldosteronism (PA) is challenging and the current screening tool, aldosterone-renin ratio, is increasingly challenged. Due to interference with immunoassays and the general high variability of plasma aldosterone levels false-positive as well as false-negative results are probably more frequent than previously assumed. Therefore, we aimed at the establishment of a reliable LC-MS/MS method to analyze aldosterone and related steroids in human urine to facilitate diagnostic workup.
Methods
450 µl urine were treated with β-glucuronidase/arylsulfatase by *Helix pomatia* and purified by off-line solid phase extraction before analysis. Chromatographic separation was carried out using an Agilent 1290 Infinity LC system equipped with binary pump, autosampler and thermostatted column compartment and a Waters Acquity® HSS PFP 1.8 µm (2.1×50 mm) column with an eluent consisting of 5 mM ammonium formate as phase A and methanol as phase B. A Sciex QTRAP 6500 mass spectrometer was used for detection of the steroids aldosterone (Aldo), tetrahydroaldosterone (THAldo), cortisol (F), 18-oxocortisol (18-OxoF), 18-hydroxycortisol (18-OHF) and 18-hydroxycorticosterone (18-OHB). Multiple reaction monitoring in positive ion mode and stable isotope labeled internal standards allowed for quantification. Complete validation will be performed according to FDA and EMA guidelines.
Results
Calibration ranges of 0.2-30 ng/ml (Aldo and 18-OHB), 1-150 ng/ml (THAldo), 2-300 ng/ml (F and 18-OHF), and 0.1-15 ng/ml (18-OxoF) have been established. First 24-h urine samples from 18 patients with PA were successfully included in the validation process and mean values were obtained as follows: cortisol 63.4 µg/24 h [IQR:27.7-95.5], Aldo 12.9 µg/24 h [IQR: 6.2-22.1], 18-OxoF 4.5 µg/24 h [IQR: 0.4-5.8], 18-OHF 123.4 µg/24 h [IQR: 21.2-138.0], 18-OHB 8.0 µg/24 h [IQR: 2.6-13.1] and THAldo 67.1 µg/24 h [IQR: 30.4-100.5].
Conclusions
We herein describe a liquid chromatography tandem mass spectrometry method for the simultaneous quantification of six steroids in human urine, which are currently validated according to FDA and EMA guidelines for application in patient care. Prospectively, the method may contribute to an optimization of the diagnostic workup of PA.

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EP30

The adrenal glands mass and hypertension with elevated levels of aldosterone: is there an association?

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Introduction
The effect of aldosterone levels on the severity of arterial hypertension was established in many studies. Changes in the level of aldosterone can lead to disorders of the cardiovascular, nervous, excretory systems. One of the factors affecting the fluctuation of aldosterone is the presence of adrenal gland mass.
Aim
To check for a correlation between the identified adrenal masses and the severity of arterial hypertension against the background of elevated aldosterone.
Materials and Methods
The study included 702 cases with changes in aldosterone levels between 2003-2022. Group 1 included 378 patients without identified formations in the adrenal glands; group 2-324 patients with identified formations. The analysis was carried out according to: gender, the severity of hypertension, the presence/absence of mass in the adrenal glands, the size of the formations.
Results and Discussion
Changes in aldosterone levels are more common in women (75.13% (284), 79.94% (259) in groups 1,2, respectively, compared with men (24.87% (94), 20.06% (65)) in groups 1, 2 respectively), ($P<0.05$). In group 1, blood pressure was measured in 326 patients, of which: normal 8.28% (27), elevated 23.62% (77), stage 1 25.46% (83), stage 2 42.64% (139); in group 2, BP was measured in 319 patients, of which: normal 7.84% (25), elevated 2.82% (9), stage 1 37.30% (119), stage 2 52.04% (166). Adrenal formation was detected in 46.15% (326) of them in the right 36.20% (118), in the left 50.92% (166), in both 12.88 (42), 53.85% (378) were not detected. In group 2, formations of the right adrenal gland that were less than or equal to 1 cm accounted for 5.08% (6), more than 1 cm 94.92% (112); formations of the left adrenal gland that are less than or equal to 1 cm were 10.84% (18), more than 1 cm 89.52% (148). The change in fluctuations in the level of aldosterone in comparison of the two groups: aldosterone in group 1 is increased by 28.25% (87), normal 70.45% (217), decreased by 1.3% (4). Aldosterone in group 2 increased by 15% (45), normal 84% (252), decreased by 1% (3).
Conclusions
1. Changes in aldosterone levels are more common in women than men in both groups. 2. In both groups, there is an increase in BP. 3. An increase in BP to stages 1,2 is more common in group 2. 4. Formations in the left adrenal gland are more common. 5. Formations are more often larger than 1 centimeter.

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EP31

Exploring experiences of patients with Adrenal insufficiency (AI) in managing adrenal crisis using parenteral hydrocortisone: A qualitative study

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Background
Adrenal insufficiency (AI) poses a significant health burden on patients, their families, and the healthcare system. Cost of illness for this patient population is four times higher than the general population. Hospital admissions due to adrenal crisis (AC) form a considerable proportion of this cost. Almost 1 in 200 patients die from AC. One in 12 patients with AI are hospitalised at least once a year following an acute AC episode if not treated promptly with parenteral hydrocortisone. Previous studies reported barriers to patient self-management at patient- and clinician- or service-level such as inadequate knowledge from patients and healthcare professionals, illness perceptions, delays in treating adrenal crisis. Out of hospital treatment of an adrenal crisis involves administration of hydrocortisone sodium phosphate (Efcortesol–liquid ampoule) or hydrocortisone sodium succinate (Solu-Cortef–powder vial) which require up to 20 sequential steps to prepare and administer intramuscularly. This can present significant challenges for patients whose health status is already severely compromised due to adrenal crisis.
Research Questions
What are the experiences of patients with AI on the management of an adrenal crisis? What are the barriers and enablers to managing adrenal crisis with the current hydrocortisone injection device?
Methods
This is a Qualitative research study using semi-structured 1:1 online interview for data collection. Adult patients with primary or secondary adrenal insufficiency and with a history of having experienced an adrenal crisis in the past 3 years are recruited via Pituitary Foundation and Addison's Disease Self-Help Group in the UK. The study is underpinned by the COM-B (Capabilities, Opportunity, Motivation–Behaviour) behaviour change Model. A convenience sampling approach will be adopted aiming to recruit 12-15 participants by end of March 2023. Interviews will be conducted online via a secure University Zoom account, transcribed verbatim and will be analysed using deductive thematic analysis with COM-B as the framework for analysis.
Outcomes
The aim is to provide an understanding on the experience and perception of patients with AI in managing AC with the use of hydrocortisone injection device. Identifying and understanding the barriers and enablers in managing AC, will inform guidance for further improvements in patient self-management strategies in preventing and managing AC.

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EP32

Hereditary and sporadic pheochromocytoma: Comparison of clinical and biological features

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Introduction
Pheochromocytoma is a rare neuroendocrine tumor derived from the adrenal medulla characterized by a high potential of production of catecholamines. The majority of pheochromocytomas are sporadic. However, recent studies show an increasing incidence of hereditary forms.
Patients and methods
This is a retrospective descriptive study including 30 patients with pheochromocytoma followed-up in the Endocrinology-Diabetology and Nutrition Department of the University Hospital Center of Mohammed-VI-Oujda in Morocco.
Results
Among 30 patients with pheochromocytoma, 22 cases (13 females and 9 males) had a sporadic form, and 8 patients (6 females and 2 males) had an hereditary form, associated with multiple endocrine neoplasia type 2 in 7 patients and Von Hippel-Lindau disease in only one case. Hereditary forms were confirmed genetically in 5 patients. The mean age was lower in the hereditary group compared with the sporadic group (35.4 ± 12.5 years vs 51.8 ± 17.1 years respectively). Hypertension was noted in 15 cases with sporadic pheochromocytoma, 8 of which had cardiovascular complications ; however, in the hereditary group, only one case had hypertension without cardiovascular repercussions. Menard triad, was more frequent in the sporadic cases (63.6% vs 37.5%). Hereditary pheochromocytomas, compared to the sporadic forms, had lower 24-hours urinary metanephrines (2.51 vs 44 times upper limit of normal), represented mainly by elevated normetanephrines compared to metanephrines in both groups.
Conclusion
Hereditary pheochromocytomas are becoming more and more frequent. A genetic testing should be offered to patients with pheochromocytoma to allow a more rigorous follow-up with avoiding recurrence and for an early detection of the disease in relatives, in purpose to reduce morbidity and mortality given the risk of additional tumors.

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EP32A

Clinical case of apparent mineralocorticoid excess

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Background
Apparent mineralocorticoid excess (AME) is an autosomal recessive disorder, caused by a homozygous or compound heterozygous mutation in the 11β-hydroxysteroid dehydrogenase type 2 (*HSD11B2*) gene. Mutated HSD11B2 does not inactivate cortisol, which has a similar affinity to mineralocorticoid receptors (MR) but approximately 100 times higher plasma level, than aldosterone. Excessive stimulation of MR leads to severe childhood hypertension, hypokalemia, metabolic alkalosis, low plasma renin activity and aldosterone level.
Clinical case
A male patient was born weighing 2,6 kg at 36 weeks of gestation from healthy consanguineous parents. At 1 year of age, laboratory data revealed hypokalemia (2,2 mmol/l), without the effect of intravenous potassium infusions. At 2 years of age, he presented hypertension, polyuria, polydipsia, hypokalemia, and metabolic alkalosis. AME was suspected and spironolactone treatment was started. At 12 years of age, due to lack of permanent effect of MR antagonists (spironolactone 200 mg/day, eplerenone 50 mg/day), the dexamethasone was added. The diagnosis was confirmed in the Department of hereditary diseases in the Endocrinology Research Centre (ERC) by identifying the homozygous mutation c.911A > G (p.His304Arg) in *HSD11B2* gene. In 2022, at 19 years of age, the patient was admitted to the adult department of ERC with uncontrolled hypertension, polyuria, polydipsia, and distal muscular weakness. He received eplerenone 50 mg/day, dexamethasone 1 mg/day, potassium supplements, amlodipine 5 mg/day. Potassium level was 2,2 mmol/l on admission. We changed eplerenone to spironolactone 150 mg/day, decreased the dose of dexamethasone to 0.5 mg/day, and replaced amlodipine with enalapril 20 mg/day. Thus, we achieved normalization of the blood pressure (BP) and potassium levels. Taking into account the long intake of glucocorticosteroids, we performed dual-energy X-ray absorptiometry and revealed bone mineral density below the expected range for age (Z-score: femoral neck -2.7 SD, L1-L4 -2.5 SD). In addition, secondary hyperparathyroidism due to vitamin D deficiency and high bone turnover markers (osteocalcin - 175.5 ng/ml, C-terminal Type I Collagen Telopeptide 4.1 - ng/ml) were detected. We recommended cholecalciferol and antiosteoporotic therapy (alendronic acid 70 mg/week, calcium carbonate 500 mg/day).
Conclusion
The goal of treatment is to control BP and correct electrolyte disturbance. We consider MR antagonists (high doses might be used) or amiloride/triamterene to be the first line treatment. Dexamethasone suppress endogenous cortisol secretion, but also reduces potassium level and has major adverse effects with long-term therapy. Thus, low-dose dexamethasone therapy should be initiated only when MR antagonists and other antihypertensive agents are low effective.

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EP33

A case of Merkel cell carcinoma in the CNC 1 (Carney complex 1) gene positive family with a rare component of the Carney complex

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Introduction
CNC (Carney complex) is a rare inherited autosomal dominant syndrome characterized by prominent pigmented lesions on the skin and mucosal surfaces, cardiac and noncardiac myxomatous tumors, and multiple endocrine neoplasms. About 70% of cases have a family history, while the remaining 30% occur sporadically as a result of de novo mutation. Two genetic loci linked to CNC have been found: the CNC1 gene on chromosome 17q22-24, which encodes the regulatory subunit (R1a) of protein kinase A (PRKAR1A) and is responsible for 2/3 of cases, and the CNC 2 gene is responsible for 1/3 of cases. The "CNC2" gene encoding the PKA (protein kinase A) catalytic subunit located at 2p16. Because clinical manifestations vary even within families, so-called "sporadic" cases require careful clinical evaluation by first-degree family members. Major, complementary and suggestive or possibly associated with CNC, but not diagnostic criteria for the disease are used for diagnosis. Endocrine neoplasms due to adrenal, pituitary gland tumors, or testicular tumors are the most common systemic manifestations of CNC.
Case
A 63-year-old female patient diagnosed with operated Merkel cell carcinoma was examined for primary hyperparathyroidism.The patient had hypercalcemia, hypophosphatemia and elevated parathormone since 2018, and the last corrected Ca-11.5 (8.8-10.6 mg/dl), P -2.4 (2.8-4.1 mg), PTH -146 (14-72 pg/ml), vitamin D-10.2 (30-100 ng/ml), 24-hour urinary calcium was 167.75 (100-300 mg). The bone mineral density was reduced. Ultrasound revealed parathyroid adenoma and multinodular goiter (MNG). Parathyroid scintigraphy revealed increased activity uptake. PRKAR1A gene mutation was positive in 2 daughters and 1 granddaughter of the patient, and her granddaughter had been operated for bilateral adrenal cushing. The patient had a nonfunctional pituitary microadenoma and bilateral adrenal nodular hyperplasia. The patient was operated for parathyroid adenoma and the pathology was compatible with adenoma. In the pathology of the nevus removed from the patient's neck who had congenital nevi, was found melanocytic nevus. PRKAR1A gene mutation was negative. Other genetic analyzes associated with CNC could not be performed. Carney complex was considered in the patient because the patient had 1 major (bilateral adrenal nodular hyperplasia), 1 complementary (positive PRKAR1A gene mutation in first-degree relatives) and criteria suggestive of CNC (congenital nevi, MNG, family history of Cushing's syndrome).
Conclusion
The highest risk of death in CNC is associated with heart disease, particularly cardiac myxomas and complications of cardiac surgery. Other causes of death include metastatic or intracranial psammomatous melanotic schwannoma, carcinoma, or metastatic tumors.

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EP34

Incidental diagnosis of bladder paraganglioma: A case report

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Introduction
Paraganglioma is a rare neuroendocrine neoplasm which tends to develop in the extra-adrenal glands. Paraganglioma in the bladder is extremely rare and accounts for 0.06% of all bladder tumors Herein we report a case of paraganglioma that was mistaken for urothelial carcinoma and revealed by an intra-operative hypertensive crisis with bradycardia.
Case presentation
A 48-year-old woman was referred to the urology department for intermittent terminal hematuria. The medical history included primary hypothyroidism and uterine Fibroids. On examination the patient appeared well built, normotensive with a heart rate of 78 bpm. Orthostatic change in blood pressure was not documented. Urinalysis revealed full field RBC and urine culture was negative. Ultrasound and Computerized tomography urogram revealed a 2.5-cm solid mass confined to the posterior wall of the bladder and an additional focal liver lesion that the dynamic enhancement pattern recall a hemangioma Decision was made to go for transurethral resection of tumor. Early during the resection, her blood pressure started to raise up to 220/110 mmhg and her heart rate decreased to 35 bpm So the procedure was held. Post operatively, her blood pressure was observed for 24 hours and showed tendency toward hypotension. Her heart rythm was monitored for 24 hours and it was normal. The pathological picture of the resected biopsy confirmed the diagnosis of Paraganglioma of urinary bladder. The 24-hour urine study revealed elevated levels of norepinephrine (0.5 nmol/l), epinephrine (0.16 nmol/l). MIBG scintigraphy detected a mass confined to the bladder without any obvious multicentricity. Six months later, the patient underwent radical removal of the tumor after being treated with a 10 day course of α and B blockade and adequate hydration. Post surgical MIBG scan didn't detect any functional lesion. In twenty-five months follow-up, patient's blood pressure, urinary VMA and epinephrine remained normal.
Conclusion
Urinary bladder paraganglioma is an extremely rare entity. The classical triad of episodic hypertension, hematuria and post-micturition syncope is virtually diagnostic, but is very rare. Our patient presented with hematuria but no hypertension. The correct preoperative identification of paraganglioma is important. However, it is often overlooked because of its rareness. Unsuspected ones may result in intraoperative hypertensive crises, as in our case, and greatly increase the perioperative mortality forcing the surgeon to terminate cystoscopic tumor resection. This case highlights variable presentation of paraganglioma, importance of having a high index of clinical suspicion for early recognition and prompt management.

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EP35

A patient guide for pregnancy in 21-hydroxylase deficiency

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Background
Affected patients with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CAH) are often insufficiently informed about disease-specific aspects of reproduction. Reasons for lower fertility rates in female patients with CAH are hormonal dysregulations, anatomical changes resulting from virilized genital surgeries and psychosocial and psychosexual factors. Fecundity, however, is comparable to the normal population. Male patients with CAH also have comparable fecundity under optimal therapy, but testicular adrenal rest tumors (TART) and adrenal androgen excess can negatively affect spermatogenesis. As long as optimal therapeutic control is achieved, course and outcome of pregnancies is not affected.
Objective
Due to the discrepancy between fertility and fecundity in patients with classic CAH, our aim was to develop a patient guide that informs female and male patients with CAH about disease-specific aspects of fertility and pregnancy. It can also be used for patient education by nurses and physicians.
Design and Methods
In order to develop the most detailed and helpful patient guide for CAH patients of childbearing potential, a literature research was conducted. The research included the basics of CAH, fertility and fecundity in male and female CAH patients, prenatal dexamethasone therapy and important factors to consider before and during pregnancy. The information was summarized and used to develop expert-based patient guidelines.
Results
Two separate leaflets were developed addressing sex-specific aspects of reproduction for both male and female patients with classic CAH. Based on the DSD-Life study, which demonstrated lower birth rates in patients with CAH and an impairment in psychosocial and psychosexual functioning, patients are now educated about factors that may affect fertility and fecundity. Further considerations during pregnancy planning are also addressed. The brochure also contains information on clinical check-ups during pregnancy.
Conclusions
A leaflet containing information on disease-specific aspects of reproduction was developed for CAH patients. It aims to convey information on optimal treatment, genetic counselling and prenatal dexamethasone therapy in order to prevent unjustified worries, uninformed decision-making and suboptimal treatment. The extent to which the developed brochures are helpful for patients with classic CAH needs to be evaluated and assessed in future studies.

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EP36

Adrenal incidentaloma revealing a cystic pheochromocytoma

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Introduction
Pheochromocytomas are rare neuroendocrine tumors producing catecholamines, they are usually unilateral. However, they can be located bilaterally. They still pose several problems in their diagnosis if they are associated with an adrenal cyst, which is the case in our patient.
Case Report
A 34-years-old male patient, his medical and family histories were non specific, admitted to the emergency room for lumbar pain, with no other associated signs, Abdominal computed tomography showed a well-demarcated cystic mass 86*76 mm with a thick wall in the region of the right adrenal gland and a left adrenal nodule of 15*18 mm, 24 hrs urine metanephrine and normetanephrine were significantly elevated metanephrine: 4.81 mg/24 h (0.04-0.30), normetanephrine : 8,73 mg/24 h (0.07-0.46). After adequate medical blockade and hydration, bilateral adrenalectomy has been performed endoscopically, The postoperative course was simple.Anatomopathological analysis showed a right cystic pheochromocytoma, and a left pheochromocytoma with no sign of malignancy.A genetic study was performed was without particularities. The evolution was favorable under replacement therapy with 30 mg/d of hydrocortisone.
Discussion
Pheochromocytoma is a tumor arising from adrenomedullary chromaffin cells that commonly produce one or more catecholamines: Epinephrine, Norepinephrine and Dopamine. Pheochromocytoma can present as cystic lesions, which may mislead the diagnosis. Pheochromocytoma should be considered in patients presenting with non specific symptoms and an incidental cystic adrenal mass, even in the absence of hypertension. A typical solid pheochromocytoma can be easily diagnosed with available diagnostic methods. However, it is difficult to diagnose cystic pheochromocytoma since it structurally resembles a benign adrenal cyst. Structural imaging may be inconclusive. Functional imaging like MIBG scan is essential to prove the presence of sympatho-adrenal tissue.
Conclusion
In any patient presenting with abdominal pain, and adrenal cystic lesion, pheochromocytoma should be suspected, because it is a rare entity and is mostly asymptomatic, and complete with a genetic study in case of bilateral involvement.
Reference
1. J Clin Diagn Res. 2016 Nov; 10(11): OD09–OD10.

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EP37

Giant Cystic Asymptomatic Pheochromocytoma

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Introduction
Giant and cystic catecholamine-secreting tumors are usually asymptomatic and detected incidentally during imaging. A simple mobilization of the tumor can cause the release of catecholamines into the blood and is therefore associated with high morbidity and mortality. Here, we aimed to present a patient with a 13 cm mass in the left adrenal gland and diagnosed as giant cystic pheochromocytoma.
Case Report
A 62-year-old male patient presented with left flank pain and frequent urination for 6 months. Abdominal computerized tomography (CT) showed a 133*78 mm

non-adenoma mass with a density of 50 HU (Hansfield Unit) and containing cystic-solid areas in the left adrenal gland. There were no symptoms or signs suggestive of pheochromocytoma such as headache, palpitation, flushing, excessive sweating and chest pain. He had type 2 diabetes and coronary artery disease for 7 years, but he did not have hypertension. On examination, blood pressure and pulse measurements were normal. Ambulatory blood pressure measurements were also normal. In laboratory results, plasma metanephrine level was 975.66 pg/ml ($<$90) and normetanephrine was 1204.42 pg/ml ($<$180), urine metanephrine was 4162.77 µg/24 h(50-250) and normetanephrine was 6170.14 µg/24 h (100-500). Hyperaldosteronism and Cushing's screening tests were normal. F-18 FDG PET/CT was performed to rule out malignant pheochromocytoma, no metastasis was detected. Adequate alpha blockade was achieved with doxazosin and left adrenalectomy was performed by an experienced surgical team. No perioperative blood pressure fluctuation was observed. On pathological examination, tumor size was 13.5*8.9*8.7 cm and weight was 274 grams. Macroscopically, it was a well-circumscribed brown mass containing cystic areas with multiple septations. In microscopic examination, there was no atypical mitotic activity, no significant pleomorphism and no increase in cellularity. There was no extraadrenal and vascular invasion, but capsule invasion was present. In the immunohistochemical examination, there was staining with chromogranin A and synaptophysin, and the ki-67 index was $<$1%. The diagnosis of pheochromocytoma was confirmed, and he was followed closely due to the large size of the tumor and capsule invasion.

Conclusion

Giant cystic pheochromocytoma is a rare entity and is mostly asymptomatic. Pheochromocytoma should be considered in the differential diagnosis of retroperitoneal tumors in patients with nonspecific symptoms and adequate therapy should be given to increase perioperative safety. It should be noted that the only curative treatment of such tumors is surgical resection.

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EP38

Bilateral pheochromocytomas-recurrence and adrenal insufficiency rate related to surgical technique and genetic status

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Introduction

Bilateral pheochromocytomas (PHEOs) most often occur as components of hereditary syndromes: MEN2A, VHL disease or neurofibromatosis. The best surgical technique in such cases is yet disputed between cortical sparing or total adrenalectomy. Two important complications are related to each surgical technique: adrenal insufficiency (AI) or recurrence-which one is more harmful for the patient?

Aim

To evaluate the complications (recurrence, AI) rate reported to surgical technique and to genetic status.

Material and Methods

We retrospectively retrieved data of 103 patients diagnosed with PHEOs in a tertiary centre from Romania and identified patients with bilateral disease.

Results

We identified 11 (10.6 %) patients with bilateral disease; 8 synchronous, 3 metachronous. Mean age at diagnosis was 32$\pm$24 y.o; 3 (27.3%) patients had pediatric age at diagnosis; 6 women, 5 men. Eight patients presented with benign PHEO, 3 with malignant disease at diagnosis. Two had adrenergic pattern, 7 noradrenergic, 2 no info. Mean tumor diameter was 47.8$\pm$3 mm. Seven patients had hereditary disease - MEN2A (5), VHL (2), 4 no info. Median follow-up duration was 9 (1-41) years. The patients' outcome reported to surgical technique: 5 had cortical sparing-(3 developed AI and 1 recurrence); 3 patients had total adrenalectomy-(both had AI, 1 recurrence); 1 patient had total unilateral adrenalectomy-contralateral tumor impossible to operate (1 recurrence); 2 no info (1 exitus, 1 lost to follow-up). The outcome reported to genetic status: from 5 patients with MEN2A, 1 had recurrence after total adrenalectomy. In patients with VHL we found 2 recurrences at 7 (bilateral) and 24 years (unilateral), at the same patient after subtotal adrenalectomy. The rest four patients without documented mutations had no recurrence. Overall, in our cohort we found a **27.2 % recurrence rate** (2 patients-3 recurrences, 1 MEN2A, 1 VHL) after 1 total adrenalectomy, 1 cortical sparing. **50 % of patients with cortical sparing had AI and 100% of patients with total adrenalectomy had AI**.

Conclusion

Cortical sparing does not always assure a normal cortical function. There are some factors that should be evaluated before choosing the proper surgery technique including tumor size, the ability to secure vascular supply to the remaining adrenal cortex and the likelihood of a predisposing mutation leading to high risk of recurrence/malignancy in the future. Patients with RET mutation have a higher risk of recurrence and multiple tumors in the same adrenal, therefore, total adrenalectomy is the best option for them.

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EP39

"Adrenal Giants" Review of adrenal masses $\geq$ 10 cm detected and treated during a 10- year period at the University Hospital Southampton NHS Foundation Trust, United Kingdom

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Introduction

The aim of this project was to review all adrenal masses $\geq$ 10 cm managed in our organisation over a 10-year period (2012-2022).

Results

20 adrenal masses $\geq$ 10 cm in maximal diameter were identified (range 10-32 cm, average 16.6 cm, 6 above 20 cm and one above 30 cm). Age at presentation was 17-80 y (mean 56.3 y, 50% F). Duration of symptoms: 1 day-18 months, mean 7.5 months with 6 presenting acutely. Follow-up period: 1 month-122 months, mean 35 months. Aetiology: 11/20 Adrenocortical carcinoma (ACC), 2/20 presumed ACCs, 7/20 as follows: 15 cm malignant melanoma (MM) metastasis (met) presenting 6 years post pT1N0M0 skin MM excision; growing MM metastasis (12 cm) despite immunotherapy; renal cell carcinoma (RCC) met in metastatic RCC (4 cm ipsilateral and 13 cm contralateral adrenal met); 10 cm pheochromocytoma [PASS 12, pT2(R0)N0M0] presented with acute coronary syndrome; 18 cm myelolipoma presented with acute abdomen due to intralesional haemorrhage; 13 cm adrenal cyst and 29 cm well-differentiated retroperitoneal liposarcoma. 17/20 (85%) had malignant aetiology. 11/20 (55%) alive at time of abstract submission. ACC in 13/20: 7/13 found to have hormonal hypersecretion (4 cortisol, 1 oestradiol, 1 combined cortisol, aldosterone & androgens). 2/13 presented with symptoms of hormone excess (gynaecomastia, severe hypertension), 11/13 with abdominal pain. 9/13 had surgery [2/9 surgery + mitotane, 2/9 surgery + mitotane + locoregional metastases control (with met resection, ablation, radiotherapy)], 1/13 mitotane only, 2/13 symptom control only (analgesia, laxatives). ACC staging at diagnosis: Stage 2: 6 patients (with three progressing to stage 4 within 6 months-3 years; 3 remain alive); Stage 3: 4 patients (one died within a month post diagnosis, 3 progressed to stage 4; 2 remain alive); Stage 4: 3 patients (all died within 4 months). Median overall survival of ACC cohort 20.0 months (95% CI 5.6 to 34.4).

Discussion

Some adrenal masses can reach huge proportions before their presentation. ACC was detected in 65%. Even at stage 2 at diagnosis, mortality and risk of progression to metastatic disease was very high. Prognosis at stage 4 at diagnosis is extremely poor and all died within 4 months post presentation. Ipsilateral adrenal metastases in RCC can occur in 6-29% especially in pT3, but bilateral adrenal or contralateral metastases are rare. Large 13 cm contralateral RCC met in our patient was therefore unusual. Significant size of adrenal MM metastases at diagnosis and their resistance/escape from immunotherapy suggest that adrenal microenvironment might be a 'sanctuary site' as suggested in our two melanoma cases and literature.

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EP40

Effects of high-dose atorvastatin treatment on adrenal steroidogenesis in type 2 diabetes patients

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Introduction

Statins are widely used to prevent cardiovascular diseases. Nonetheless, reducing cholesterol, the main substrate for steroidogenesis, may impair cortisol production. The aim of our study was to assess the effect of high dose statin therapy on cortisol and dehydroepiandrosterone-sulphate (DHEA-S) levels in type 2 diabetes male patients.

Methods

This was a single-center, prospective study, during the period march 2021 - July 2022, including 60 men with type 2 diabetes mellitus, aged between 40 and 65

years, statin-free, and in whom the indication of a treatment with high dose of statin was indicated. The patients had two visits, before and six months after the daily intake of 40mg of atorvastatin. During each visit, they underwent a clinical examination and a fasting blood sample was collected for biological and hormonal measurements including cortisol and DHEA-S.
Results
The median age was 58 years (IQR: 52-62). The median body mass index was 29.5 kg/m^2. The prevalence of asthenia, anorexia, and orthostatic hypotension increased significantly after statin intake from 35%, 12%, and 17% to 38%, 23%, and 18%, respectively. A decrease of 51.1% in median LDL-cholesterol was noted after statin administration. The median serum cortisol level was 289 nmol/l (IQR: 242-384) before and 301 nmol/l (IQR: 236-357) after atorvastatin intake ($P=0.371$). The median DHEA-S level decreased significantly from 4.5 µmol/l (IQR: 2.8-6.1) to 3.8 µmol/l (IQR: 2.6-5.6) after statin intake ($P=0.005$). The reduction of DHEA-S was significantly correlated with the reduction of LDL-cholesterol ($r=0.262$, $P=0.043$).
Conclusion
Long-term high-dose atorvastatin treatment in patients with type 2 diabetes did not impair serum cortisol levels but reduced DHEA-S levels.

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EP41

The role of CRH test in predicting the efficacy of unilateral adrenalectomy in Bilateral Macronodular Adrenal Hyperplasia

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Background and Aim
Bilateral Macronodular Adrenal Hyperplasia (BMAH) is a rare form of adrenal Cushing's syndrome (CS). The treatment of choice in patients with BMAH and overt CS is bilateral adrenalectomy (B-Adx), which however implies lifelong glucocorticoid and mineralocorticoid replacement therapy. Unilateral adrenalectomy (U-Adx) has been proposed as an alternative to B-Adx, especially in case of clearly asymmetric adrenal size. Our aim was to determine predictive factors (e.g. gender, age, mutation status, response to dynamic tests) for remission after U-Adx in BMAH patients.
Patients and Methods
BMAH patients undergoing U-Adx for overt CS were considered eligible. Overt CS was defined as urinary free cortisol (UFC) $\geq$2 times the upper limit of normality (ULN) and unsuppressed serum cortisol after overnight 1-mg dexamethasone (DST). After U-Adx, BMAHremission was defined as UFC$<$ ULN without additional therapy. BMAHactive were patients with UFC$>$ULN who required medical therapy or additional surgery for B-Adx. 9 patients were mutated in ARMC5 gene,12 were wild-type, while 2 have not been studied. We compared patients considering therapeutic outcome (BMAHremission vs BMAHactive), gender, ARMC-5 mutational status, baseline UFC ($\geq$2 or $>$3 times the ULN), overnight 1-mg DST (50-138 or $>$138 nmol/l), and the delta ACTH increase to CRH (positive test response: $>$50%).
Results
Twenty-three patients with U-Adx for overt CS were enrolled (69% females, mean age 55 years). According to genetic workup, 9 patients were ARMC5 mutated (wild type, $n=12$; no genetic workup, $n=2$). After U-Adx, 17 patients (74%) had remission for at least 18 months. BMAHremission and BMAHactive groups were comparably distributed regarding gender ($P=0.621$), UFC ($P=1.000$), overnight 1-mg DST ($P=1.000$), and ARMC5 status ($P=0.611$). The CRH test was performed in 15 patients (65%). Absence in ACTH response to CRH was observed in 6 patients (BMAHactive after U-Adx, $n=3$; recurrence after initial remission, $n=2$; CS in remission, $n=1$. The other 9 patients showed a positive test response, (BMAHremission after U-Adx at last follow-up, $n=8$; recurrence after initial remission, $n=1$). A significant correlation between ACTH response to CRH and positive outcome after U-Adx was found ($P=0.011$).
Conclusions
Remission rate from overt CS after U-Adx was higher in patients with a positive ACTH response during the CRH test (8/9 (89%) vs 1/6 (17%) in non-responders). We therefore suggest to perform the CRH test during the preoperative diagnostic workup for estimating the therapeutic outcome of U-Adx

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EP42

Circadian fluctuations of acylcarnitines and sphingomyelins when measured in serum and in dried blood spots

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Background
Acylcarnitines and sphingomyelins are key players of lipid metabolism at cytosolic, vesicular and cell membrane level. Their metabolism was found deranged in diseases of the hypothalamus-pituitary-adrenal axis. Little information is available about levels of these compounds in the bloodstream and their circadian fluctuations. Dried blood spots (DBS) allow multiple autonomous and painless collections per day. However, poor biological validation data are available about lipid measurement in DBS.
Aim
To evaluate acylcarnitine and sphingomyelin levels and daily variations in paired serum and DBS collections.
Methods
Three women and three men aged 26-50 y were enrolled. All were healthy, normal weight and followed a Mediterranean standardized diet for one week, ending with the collection day. Serum and DBS were obtained 30 min before and 2 h after breakfast (7.30), lunch (13.30) and dinner (19.30). Forty acylcarnitines and 15 sphingomyelins were quantified by flow injection - tandem mass spectrometry.
Results
Twenty-four acylcarnitines were undetectable, 6 were only detectable in serum, 2 only in DBS and 8 in both; mean levels ranging 0.104-40.5 µM in serum and 0.160-21.8 µM in DBS. Four acylcarnitines were higher ($P<0.001$), whereas carnitine was lower ($P=0.003$) in DBS vs serum. Direct correlations between DBS and serum levels were observed for 7 analytes (P: $<$0.0001-0.019), with strongest correlations displayed by carnitine ($R=0.797$), butyrylcarnitine ($R=0.714$) and propionylcarnitine ($R=0.686$). Serum propionylcarnitine, valerylcarnitine, octanoylcarnitine, dodecanoylcarnitine and tetradecenoylcarnitine showed significant daily variations (P: 0.002-0.038), with positive quadratic or negative linear trend. Butyrylcarnitine, acetylcarnitine and hexadecanoylcarnitine showed significant daily variations in DBS (P: 0.009-0.037), with negative linear trend. All sphingomyelins were detectable, ranging 0.197-119.9 µM in serum and 0.281-136.5 µM in DBS. Five and 6 molecules were higher and lower in DBS vs serum, respectively (P: $<$0.001-0.026). Nine sphingomyelins displayed direct correlations between DBS and serum levels (P: $<$0.0001-0.028), with strongest correlations displayed by sphingomyelins(SM)-OH-C22:2 ($R=0.790$), SM-C16:1 ($R=0.760$) and SM-C20:2 ($R=0.690$). No analyte fluctuations were found in serum, whereas significant daily changes were observed in DBS for 11 sphingomyelins (P: $<$0.001-0.036), mostly with negative linear trend. Strongest variations were observed for SM-OH-C16:1, SM-C20:2, SM-C24:0, SM-OH-C24:1, SM-C26:0 and SM-C26:1.
Conclusion
Despite significant correlations between serum and DBS levels, acylcarnitines and sphingomyelins showed different patterns of circadian fluctuations in the two matrices. This may depend on the different distribution of individual molecules in soluble and cellular bloodstream fractions. Further studies are necessary to establish the relevance of serum and DBS measurements for the characterization of circadian rhythm imbalances.

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EP43

The effect of long-term treatment of glucocorticoid in adipogenesis/-turnover in epididymal cells

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Cushing syndrome is a comorbid condition resulting from long-term exposure to glucocorticoids (GC). It affects body fat composition in various parts of the body. Since each fat depot has a distinct response to glucocorticoid exposure, we wanted to understand adipose tissue turnover. In order to reproduce the disease state, we used a rodent model recapitulating Cushing syndrome. We inserted subcutaneous mini pumps in the dorsal area of rats to infuse Dexamethasone at a rate of 187.5 µg/day, for 4 months. Dexamethasone is a synthetic analog of human cortisol. We collected different fat depots. We observed that total epididymal (EP) fat weight was proportionately lower as the total body weight of the animal. Similarly, the

adipocyte size and volume were negatively redistributed. We also found that exposure to Dexa for 48 hrs, decreased incorporation of glycerol, fatty acids and lipids. There was an increase of glycerol release, from epididymal adipocytes, which likely resulted in decrease in lower EP mass. We then explored the mechanism of adipocytes turnover in Dexa treated animals. We found that adipogenesis and apoptosis pathways were altered resulting in the redistribution of the fat. We observed that EP tissue had lower phosphorylation of caspase 3, 8 and 9 in Dexa treated compared to untreated group, while adipocytes from Dexa-induced rats showed upregulation of adipogenic markers, as PPARγ, CEBPα, and SREBP1. However, pre-adipocytes derived from Dexa treated animals revealed lower lipogenesis. The resistance to incorporate lipids might be affecting the commitment of those cells to matured. In summary, the mature adipocytes from EP fat tissue have higher adipogenic markers and low activation of cell death pathways which could explain the phenotype of Cushing syndrome.

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EP44

Implementation of a new adrenal venous sampling (AVS) protocol for primary aldosteronism: early data from a single tertiary centre

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Primary aldosteronism (PA) is the most common cause of endocrine hypertension. Following biochemical confirmation of aldosterone excess, adrenal venous sampling (AVS) is the gold standard investigation to lateralise the source of aldosterone hypersecretion in patients deemed suitable for potential adrenalectomy. AVS has been performed for all suitable patients with a diagnosis of PA in Beaumont Hospital since implementation of a new protocol involving collaboration between Endocrinology, Chemical Pathology and Interventional Radiology in 2021. We aimed to review the outcome of all AVS procedures in Beaumont Hospital between November 2021 and December 2022, with a focus on rates of successful cannulation and the incidence of unilateral versus bilateral disease. We identified 13 patients with PA who were referred for AVS between November 2021 and December 2022. Median age was 46 [IQR 37–51 years] and 38.5% were female. Patients had hypertension for a median of 15 years [IQR 6–25 years]. 53.8% had a history of hypokalaemia. Confirmatory testing with saline suppression test was performed in 10 of 13 cases. The median post saline suppression aldosterone level was 498.5pmol/l [IQR 442 -732pmol/l]. Imaging reported a unilateral adenoma in 61.5% of cases, with a median adenoma diameter of 2 cm [IQR 1.05–3.05 cm]. Sixteen AVS procedures were performed, as 3 patients required a repeat procedure. Bilateral adrenal vein cannulation was successful in 10 of 16 cases [62.5%]. Results of one patient who was successfully cannulated were disregarded as she had taken oral Prednisolone the day prior to the procedure. All patients were discussed at a multidisciplinary team meeting. Unilateral hypersecretion was confirmed in 3 of 9 cases [33.3%]. Out of 5 patients with bilateral disease on AVS, 2 had a unilateral adenoma on imaging. One patient was referred for repeat procedure due to discordant results. AVS is the gold standard means of differentiating unilateral from bilateral forms of PA. Early success rates within the first 12 months in Beaumont Hospital are in line with accepted international standards and will continue to improve with accumulated experience and case throughput. AVS has helped to identify patients suitable for adrenalectomy in our centre, while inappropriate adrenalectomies have also been avoided in a subset of patients.

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EP45

A rare case of a juxta-adrenal schwannoma presenting as an adrenal mass

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Background
Retroperitoneal Schwannomas are rare and generally benign tumors originating from the neural sheath. In particular, juxta-adrenal schwannomas may be misdiagnosed as adrenal tumors due to their location and radiological characteristics.
Case Presentation
A 40-year-old female patient referred to our outpatient clinic owing to a left suprarenal mass of 35 mm incidentally discovered in an enhanced CT. She was asymptomatic and the clinical examination was unremarkable. The mass had an absolute wash-out of 80% in the enhanced CT and presented 36UH in the non-enhanced CT. In the MRI the lesion was hypointense on T1 sequences, with a slight loss of signal on out-of-phase sequences, with a heterogeneous signal on T2 sequences, diffusion restriction and progressive enhancement after intravenous contrast administration. Therefore, showing indeterminate characteristics. The FDG-PET-CT revealed a slightly hypermetabolic mass (SUVmax 5.14), without uptake in the MIGB-123I scintigraphy. The hormone evaluation ruled out a hypersecretory adrenal mass. The MRI performed after 8 months of follow-up showed a growth of 2 mm. She was diagnosed with an indeterminate adrenal mass and underwent laparoscopic adrenalectomy. After the surgery, she presented among the complications, a chylous fistula that resolved with drainage, parenteral nutrition, and a low-fat diet. The histopathological and immunohistochemistry findings reveal a juxta-adrenal cellular schwannoma. It was a rounded, well-defined, and non-encapsulated lesion of 3.5*2.7*2 cm diameter, located in the surrounding adipose tissue of the adrenal gland without contacting it. It had a cellular "Antoni A" pattern, no necrosis, occasional mitosis figures, and lymphoid aggregates at the periphery of the lesion. The cells were positive for Vimentin, S 100 and SOX10, and the Ki-67 index was 5%. In the follow-up CT at 6 months, there were no signs of recurrence.
Conclusion
Juxt-adrenal Schwannomas should be included in the differential diagnosis of adrenal incidentalomas. Being a mass next to the adrenal gland with indeterminate radiological features, often it is misdiagnosed as adrenal carcinoma or atypical adenoma. Complete surgical resection is the treatment of choice and histology and immunohistochemistry confirm the diagnosis.

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EP46

Acute Bilateral Non-Traumatic Adrenal Haemorrhage; a case series

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Adrenal haemorrhage is a serious condition that can result in adrenal insufficiency, shock, acute adrenal crisis, and mortality if not managed with adequate treatment. Hereby we present two cases of non-traumatic bilateral adrenal haemorrhage highlighting their management during the acute phase.Case 1: 57 year old female presented due to chest pain, palpitations and troponin rise with a background history of antiphospholipid syndrome on anticoagulation. She was treated as acute myocarditis. A CT abdomen was done after an episode of abdominal pain which showed bilateral adrenal haemorrhage. She remained haemodynamically stable with no drop in haemoglobin levels. Anticoagulant effect of warfarin was reversed with intravenous phytomenadione and dried prothrombin complex. She developed an acute left leg DVT after a couple of days and was managed on the lines of catastrophic antiphospholipid syndrome treated high dose of prednisolone and mycophenolate mofetil. Subsequent short synacthen test done after weaning of prednisolone confirmed adrenal insufficiency and she has maintained on replacement hydrocortisone. Repeat cross-sectional imaging was planned in three months to confirm resolution and exclude underlying adrenal pathologyCase 2: 55 year old male presented with right sided flank pain for one week. There was no history of trauma, weight loss, anticoagulation use and clinically no evidence of infection or sepsis. A CT abdomen showed bilateral adrenal enlargement with features in keeping with haemorrhage and small retroperitoneal rupture on the right. Given the haemodynamic stability along with stable serial haemoglobin levels, it was adjudged that non-surgical conservative management is appropriate in this case. Due to the bilateral nature of the disease he was started on replacement hydrocortisone which was subsequently stopped post a normal short synacthen test. Due to extensive past history of smoking a CT chest was conducted that showed 2 right lung lesions. His imaging was discussed in the local Lung and Adrenal MDT with a plan for short interval CT for the lung lesions followed by diagnostic investigation if required.

Biochemical test for hyperfunction and repeat cross sectional adrenal imaging was planned after 3 months of the acute phase.In conclusion, bilateral adrenal haemorrhage can be secondary to various aetiologies. These cases can be managed conservatively if there is no evidence of persistent bleeding and haemodynamic instability. Further investigations after resolution of bleeding is required to determine the functional status and reassess the lesion on imaging.

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EP47

Primary hypoadrenalism and thyroiditis in metastatic renal carcinoma in Pembrolizumab (PD-1inhibitor) and Axitinib (VEGFR inhibitor) therapy

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The association of immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) are widely and to with good effect used in the treatment of many neoplasms. Much evidence of endocrine side effects has been reported for both ICIs and TKIs especially to the pituitary and thyroid functions; however, there are few records of primary adrenal insufficiency. We report the case of a 44-year-old soldier, examined for elevated hematocrit findings. Abdominal ultrasound and thoracoabdominal CT scan revealed a left renal tumor with bilateral pulmonary nodules and right iliac lytic lesion. Underwent left nephrectomy, histology revealed a renal clear-cell renal Ca with variant renal vein invasion by sarcomatoid cells (grade 4). pT3a. Adjuvant therapy with pembrolizumab and axitinib was started. Eight weeks later fT4 serum levels were elevated (2.15 ng/dl) with suppressed TSH (0.07 mUI/l) (normal range: 0.8-1.8 and 0.35-4.6, respectively). The endocrinologist advised TPOAb and TRAb resulted present and absent, respectively; a pseudonodular picture is was detected on ultrasound and a diffuse hypocaptation is was found on thyroid scintigraphy, suggestive of thyrotoxic-onset thyroiditis. Therapy with bisoprolol alone was started; after 4 months the hyperthyroidism evolved into hypothyroidism and therapy with L-thyroxine was started. At the same time, the pituitary-adrenal axis was also studied with evidence of normal cortisol (13.5 mg/dl) and elevated ACTH serum levels (128 pg/ml) (normal range 6-28 and 0.0-46.0, respectively) suggestive of primary hypoadrenalism and cortisone acetate was started; the anti21OH Abs were negative. The patient maintained a good quality of life and given the good response of the tumor, documented by a CT scan, the oncological therapy was continued. To the restaging CT scan after 10 months of therapy, despite the excellent clinical conditions of the patient and good hormonal compensation, the presence of a right adrenal lesion of 1.6 cm was instead detected, with increased glucose metabolism on PET/CT scan 18F-FDG with clearly reduced subcentimeter lung lesions on CT scan, and nonhypermetabolic on PET/CT scan, and disappearance of the right iliac lytic lesion. Right adrenalectomy was performed. Histology revealed a clear cell renal Ca metastasis. In conclusion : 1. Immune-mediated thyroiditis with transient hyperthyroidism appeared after 8 weeks of therapy followed by hypothyroidism; 2. primary hypoadrenalism, negative for Ab21OH, appeared after 4 months of therapy; 3. good clinical, pulmonary and bone response to therapy with pembrolizumab and axitinib was obtained, but appearance at 10 months of right adrenal lesion as a heterogeneous response to therapy.

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EP48

Chronic hypopituitarism as a rare first presentation of euvolaemic hyponatraemia

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Background
Hyponatraemia is the most common electrolyte abnormality encountered in hospitals and has been independently associated with increased morbidity and mortality[1]. An appropriate work-up with guideline-based investigations and management is, therefore, crucial to allow accurate diagnosis and optimisation of patient care.
Case Presentation
A 49-year-old with no significant past medical history presented with 2 weeks of persistent nausea and lethargy, alongside worsening headaches. Sodium levels were 116 mmol/l on admission, without an apparent acute cause. Further assessment revealed secondary hypothyroidism and unrecordable cortisol levels, in keeping with hypopituitarism. Urgent MRI scanning was performed to exclude pituitary apoplexy; this ruled out haemorrhage but demonstrated a solitary pituitary lesion, likely having caused chronic pituitary failure and insidious development of hyponatraemia.
Outcome
Commencing glucocorticoid replacement therapy caused a rapid correction of sodium levels and the resolution of the patient's symptoms. Growth hormone, thyroxine and testosterone replacement were initiated, and the patient reported substantially improved quality of life, feeling 'like a new person'. Follow-up scans revealed shrinkage of the lesion, with no operative intervention necessitated.
Discussion
This case describes a rare cause of hyponatraemia and highlights the importance of maintaining open differential diagnosis for patients, given the variety of potential aetiologies. Studies have shown that misdiagnosis of chronic hypopituitarism occurs frequently; often due to poor compliance to diagnostic criteria such as those for the syndrome of inappropriate ADH hormone secretion (SIADH)[2]. Local audit of hyponatraemia work-up revealed deficiencies in comparison to the latest ESE guidelines. A subsequent literature review of published UK audits on hyponatraemia demonstrated country-wide issues with guideline adherence. When combined with the significant benefits an accurate diagnosis provided this patient, our research gives evidence to highlight a need for further work to raise awareness of hyponatraemia investigation and management amongst clinicians, in order to ensure optimal patient outcomes.
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EP49

Rare case of Munchausen Syndrome in endocrinology: artificial hypokalemia

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Introduction
An atypical manifestation of disease combined with inconsistent results of examination, long history of multiple past health care services without effect requires to consider factitious disorders.
Case report
A 46 year-old woman was suffering from episodes of severe hypokalemia (K+ 1.9 - 3.4 mmol/l (ref. 3.5-5.1 mmol/l) and hypertensive crises up to 240/145 mm Hg for 4 years. She stated that there was no clear provoking factor for these episodes and the hypertension was resistant to multicomponent treatment. Previous exams showed normal levels of aldosterone and renin, but elevated normetanephrine in 24-hour urine (1548 mg/24 h (ref. 35-445 mg/24 h)) and normal metanephrine. During the last years, the patient underwent 11 different imaging studies, including MRI of the abdomen, scintigraphy with SPECT/CT with In-111 and with MIBG, PET/CT with 68Ga-DOTA-TATE that were negative and ultrasound endoscopy and CT of the abdomen, that showed conflicting results and suspicion for two 3 mm tumors in the descending part of the duodenum or adjacent head of the pancreas. At admission, there was also slightly increased level of normetanephrine (708 mg/24 h) and normal metanephrine. During the first days of hospitalization, the patient developed severe progressive hypokalemia despite IV potassium infusions and spironolactone treatment. Blood pressure monitoring showed hypotension and no episodes of hypertension, thus antihypertensive therapy was stopped. The 24-hour urine collection also demonstrated

(Abstract EP49)

	Days of hospitalization							
	1	2	3	4	5	6	7	8
Na+, mmol/l (136-145)	136.5	137.3			137.6	139	134.8<	137.1
Cl-, mmol/l (98-107)	87.5<	92.2<			106.4	99	101.5	99.7
K+, mmol/l (3.5-5.1)	2.23<	2.46<	<2	2.9–3.3	3.27<	3.56	3.97	4.01

a high potassium level (174 mmol/24 h (25-125)). The patient denied taking any additional drugs, but diuretic abuse was suspected. The high-performance liquid chromatography–high resolution tandem mass spectrometry of the patient's serum sample confirmed the presence of torasemide. The patient was advised to consult a psychiatrist which she refused.

Conclusion

Munchausen Syndrome can be difficult to diagnose and should be suspected in cases of atypical presentation. Diagnosis should be guided by clinical reasoning as multiple laboratory and imaging studies can lead to incidental findings. Liquid chromatography–mass spectrometry can be an invaluable tool to uncover artificial disorders.

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EP50

Autonomic Cortisol-Secreting Adrenal Mass Containing Extramedullary Hematopoiesis Foci

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Introduction

Extramedullary hematopoiesis (EMH) is most commonly seen in reticuloendothelial system tissues such as liver, spleen and lymph nodes. Rarely, it can be detected in non-hepatosplenic atypical localizations such as the adrenal glands. Although the underlying mechanism is not clearly elucidated, it is suggested that the adrenal glands have hematopoietic activity in the fetal period and EMH may develop from the remains here due to chronic anemia. We aimed to present a case of myelodysplastic syndrome (MDS) presenting with an adrenal mass that secretes autonomic cortisol and contains EMH foci.

Case Report

A 67-year-old female patient was diagnosed with MDS 5 years ago and erythropoietin treatment was started due to anemia. In the abdominal magnetic resonance imaging (MRI) performed 4 years ago, a 33*25 mm adenoma with signal loss in the external phase sequence was detected in the right adrenal gland. Cortisol level was not suppressed in the 1 mg dexamethasone suppression test (DST) performed for hypercortisolemia. As a result of further investigations (Table 1), autonomic cortisol hypersecretion originating from adrenal adenoma was considered. Pheochromocytoma and hyperaldosteronism tests were normal. It was decided to follow-up because there was no indication for treatment. No significant change was observed in adenoma size and clinic in 3-year follow-up. However, in the control abdominal MRI performed at the end of the 4th year, it was observed that there was a minimal increase in the size of the lesion and heterogeneous signal loss that was not present in the previous imaging. PET CT was performed to exclude malignancy since collision tumor was prediagnosed in MRI findings, no metastasis was detected, then laparoscopic right adrenalectomy was performed. Microscopic and immunohistochemical examination revealed an cortisol-secreting adrenocortical adenoma containing EMH foci. She was referred to the hematology department due to the development of adrenal EMH due to MDS and chronic anemia.

Conclusion

The development of EMH foci due to MDS in a stable autonomic cortisol-secreting adrenocortical adenoma is not a common condition, therefore our patient is a rare case in the literature. It should be kept in mind that EMH may develop in atypical localizations in hematological diseases.

Table 1 Laboratory findings

Parameter	Result	Reference Range
Cortisol	14.39 μg/dl	
ACTH*	9.6 ng/l	<46
Mid-night Salivary Cortisol	1.19 ng/ml	0.7-2.2
Urine Free Cortisol	19.22 μg/24 h	3.5-45
2 mg DST (Liddle test)	4.92 μg/dl	

*ACTH: Adrenocorticotrophic hormone

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EP51

A primary adrenal lymphoma with a puzzling evolution: A case report

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Introduction

Primary adrenal lymphoma (PAL) is a very rare entity. Less than 200 cases have been reported. Its evolution is unfavourable even under treatment. We report a case of PAL with a falsely reassuring course unmasked by 18F-FDG PET-CT.

Observation

This is a 48-year-old female patient hospitalized with altered general condition, weight loss, fever and cytopenias. The initial thoraco-abdomino-pelvic CT scan revealed two large bilateral adrenal tumour masses (18×13.7×9.8 cm on the left, 10×9.7×5.5 cm on the right). An adrenal insufficiency was confirmed and treated. CT-guided adrenal biopsy concluded to be a diffuse large cell B lymphoma. The patient received 4 courses of chemotherapy (R-CHOP). Post-chemotherapy thoraco-abdomino-pelvic CT scan showed moderate regression of the adrenal masses (12.7×11×7 cm on the left, 9×8×6.2 cm on the right) with an estimated partial response of 62% (Cheson criteria). In view of the discrepancy between radiological improvement and persistence of clinical alteration, a complementary 18F-FDG PET-CT scan ruled in favour of a metabolic progression (Deauville score = 5): two intense hypermetabolic adrenal foci (SUVmax = 20. 68 on the left, 15.12 on the right) with locoregional invasion of the psoas (SUVmax = 12.64), external oblique (SUVmax = 17.45) and pectoralis major (SUVmax = 6.93) muscles. The patient died 6 months later.

Discussion

18F-FDG PET-CT has become the reference imaging technique for the evaluation of lymphoma extension and therapeutic response. Our case illustrates this superiority since the therapeutic response described on PET-CT was more compatible with the actual clinical evolution of the patient.

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EP52

Hyperpigmentation leading to depression in Addison's disease: Case report

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Addison's disease (AD) occurs when 90% of the cortex of Adrenal Glands is affected. Most common causes of AD are autoimmune destruction, tuberculosis, hemorrhage due to meningococcal meningitis, metastatic cancers and adrenoleukodystrophy. AD is associated with other autoimmune disorders e.g., vitiligo, type-1 diabetes or hypothyroidism. Due to non-responsiveness of adrenals to Adrenocorticotrophic hormone (ACTH), α-melanocyte stimulating hormone levels increases and its pro-hormone peptide pro-opiomelanocortin production is strongly increased causing bronze pigmentation of exposed parts of the body. Other features include fatigue, lethargy unintentional weight loss, depression, irritability, vomiting, and loss of libido.

Case presentation

A 35 year old female house wife presented in the Endocrinology department with complaints of nausea, vertigo with tiredness, lethargy with mood swings from severe depression to irritability with yelling and beating her kids at times, hallucinations at night that she will die soon and whose going to take care of her children having unintentional weight loss and darkening of knuckles, palmar creases, lips and oral mucosa and tongue for the past 3 yrs. Treated with different antiemetics and antipsychotics. Different health care providers were unable to diagnose though features were suggestive of the disease and confirmed by labs.

ACTH > 1250 pg/ml (10-60).
Serum cortisol 8 am 4.2 (5-23).
Sodium 128 mEq/l (136-146).
TSH :7.5 ulU/ml (0.4-4.2).
FT4:0.4 ng/dl (0.8-2.37).
FBS :80 mg/dl (<100).
HB: 8.8 gm/dl (12-15).
TPO antibodies positive.

Hypothyroidism also cause depression. It co-presents with AD, a condition known as Schmidt syndrome (part of Autoimmune polyglandular syndrome). Depressive symptoms were the initial and devastating presentation of patient initially being misdiagnosed, as it did in this case. Neuropsychiatric symptoms were due to pigmentation of her face and hands and was desperate to remove them by creams or lotions because her brother was getting married, so was depressed and reluctant to face the guests with darkened patches. Neuropsychiatric symptoms that occur in AD were related to normal to mildly low glucose levels and hyponatremia which may cause brain damage. Decreased glucocorticoids also effect brain and cognitive function. Resulting in an increase in neural excitability, leading to an enhanced ability to detect sensory input, and precipitate hallucinations as well as lower the threshold for psychosis.

Conclusion

AD should always be kept in mind by physicians while treating a psychiatric patient (especially in cases of depression and psychosis) who have no past or family history of psychiatric illness or who fail medical therapy for depression.

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EP53

Metabolic syndrome and primary bilateral macronodular adrenal hyperplasia

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Introduction
Primary bilateral macronodular adrenal hyperplasia (PBMAH) is a rare entity. Up to 1/3 of patients with incidental bilateral adrenal nodules presents biochemical evidence of hypercortisolism responsible for obesity, diabetes mellitus (DM), arterial hypertension or dyslipidemia. Its insidious course and nonspecific signs explain the underdiagnosis of this entity.
Objective
To describe the case of a patient with metabolic syndrome (MS) with hypercortisolism and diagnosis of PBMAH and its evolution after unilateral adrenalectomy.
Clinical Case
A 73-year-old man was referred to an Endocrinology consultation in 2013 due to incidental bilateral adrenal nodules detected in a vascular study. It is a patient with DM diagnosed at 52 years old without insulin therapy and HbA1c of 6.4%, class II obesity (weight 103 kg, Body Mass Index 36.1 kg/m^2), high blood pressure under 4 classes of antihypertensive drugs and mixed dyslipidemia. He presented a serum cortisol level post-1 mg dexamethasone suppression test and post-low dose dexamethasone suppression test of 2.70 and 2.60 µg/dl, respectively, and an aldosterone at 4 h after saline suppression test of 7 ng/dl. The urinary free cortisol measurement was 27.0 and 40.3 µg/24 h (4.3-176.0), serum cortisol (8 h) 12.50 µg/dl (4.82-19.50), ACTH (8 h) 6.61 pg/ml (ND-46) and DHEA-SO4 97 µg/dl (104.9-256.1). He performed a non-radiocontrast-enhanced computed tomography that showed a nodular thickening of the right adrenal with 24 mm and of the left adrenal with 20 mm. He maintained medical treatment due to clinical stability. In 2016 due to worsening of glycemic control, he needed insulin therapy in increasing doses (maximum 96 U/day) with a maximum HbA1c of 9.8% in December 2020. He was proposed for surgery and performed a scintigraphy of the adrenal cortex with 131 I-norcholesterol, which showed bilateral adrenal cortex hyperfunction. In 2021, he underwent right adrenalectomy with histological examination compatible with PBMAH. Three months after surgery he improved his glycemic profile (HbA1c 6.4%) and he had a 16.7% reduction in total daily dose (TDD) of insulin (80 U/day), maintaining his weight (103 kg) and his antihypertensive therapy.
Conclusion
In this clinical report, PBMAH seems to have contributed to MS previously known and the worsening of DM which is reinforced by the reduction of TDD of insulin after unilateral adrenalectomy. Considering the potential for improvement of comorbidities after surgery, there should be a high index of suspicion in the presence of MS and bilateral adrenal nodules.

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EP54

The overproduction of interleukin-6 in pheochromocytoma and its impact on systemic inflammation compared to other types of adrenal tumors

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Background
The circulating inflammatory markers and cytokines are associated with unfavorable cardiovascular and metabolic outcomes in patients with primary hypertension. Few reports demonstrated that some adrenal tumors can produce various markers of inflammation, acute phase protein and cytokines, contributing to hemodynamic and metabolic disturbances.
Objective
We aimed to study the differences in the levels of inflammatory parameters and interleukin-6 (IL-6) in adrenal tumors, and their effects to clinical presentations and outcomes.
Methods
We prospectively collected the data of 20 patients with primary aldosteronism (PA), 20 patients with pheochromocytoma (PHEO), 8 patients with mild autonomous cortisol excess and 8 patients with non-functioning adrenal adenoma in Siriraj hospital. The demographic and clinical data, radiographic finding, hormonal status, intraoperative and postoperative outcomes, and follow-up data were evaluated in this study. Inflammatory markers (complete blood count, c-reactive protein (CRP), prealbumin) and IL-6 were measured in all patients, and compared between each group.
Results
Patients with PHEO had significantly higher IL-6 levels than those with other adrenal tumors (4.4 vs 2 pg/ml, $P=0.003$). 8/20 (40%) of patients with PHEO had elevated of IL-6 than normal reference range. Of these patients with IL-6 secreting PHEO, 50% had history of unexplained fever, 88% had weight loss, and all patients had anemia. Only two patients with PA had mild elevation of IL-6, and no systemic inflammatory manifestation was demonstrated in these patients. Median size of IL-6 secreting PHEOs were larger than non-IL-6 secreting PHEO (11 cm vs 5.4 cm, $P=0.1$). Patients with PHEO had lowest prealbumin levels ($P=0.004$). No significant difference in CRP levels and white blood count levels was found among adrenal tumors. Diabetes was seen in 13(65%) patients with PHEO and significantly higher than other groups ($P<0.001$). Hospital length of stay after surgical resection was significantly longer in patients with IL-6 secreting PHEO (20 days vs 8 days, $P=0.008$). Postoperatively, IL-6 levels gradually returned to normal.
Conclusions
Adrenal tumors, especially PHEO, had the elevation of inflammatory markers and IL-6, and subsequently produced systemic inflammatory response and increased postoperative complications.

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EP55

Effect of long-term atorvastatin treatment on serum vitamin D levels in type 2 diabetes patients

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Introduction
Statins are widely used in primary and secondary prevention of atherosclerotic cardiovascular diseases. The effects of statins on vitamin D are unclear. The reduction of cholesterol synthesis, a substrate for vitamin D synthesis and the decrease of LDL, the major carrier of vitamin D in the blood, can affect vitamin D metabolism. We aimed to evaluate the effect of high dose statin therapy on serum vitamin D levels.
Methods
This was a single-center, prospective study, including 60 men with type 2 diabetes mellitus, aged between 40 and 65 years, statin-free, in whom the indication of a high dose statin treatment was indicated. The patients had two visits, before and six months after the daily intake of 40 mg of atorvastatin. During each visit, they underwent a clinical examination and a fasting blood sample was collected for biological and hormonal measurements including parathormone and vitamin D.
Results
The median age was 58 years (IQR: 52-62). Twenty-seven (45%) were obese. Thirty-one patients (52%) had hypertension. Twenty percent of participants were on metformin, 12% on insulin, and 3% on sulfonylureas. The median of LDL-cholesterol decreased significantly after statin intake from 1.1g/l (IQR: 0.9-1.4) to 0.6 g/l (IQR: 0.5-0.7), $P<10^{-3}$. Before statin administration, the median of corrected calcemia, phosphoremia and parathyroid hormone were respectively 2.3 mmol/l (IQR: 2.3-2.4), 1 mmol/l (IQR: 0.9-1), and 6.6 pmol/l (IQR: 4.9-10.2) and did not change significantly after statin intake. The median level of vitamin D was 37.4 nmol/l (IQR: 26.1–52.7) before atorvastatin therapy and 40.5 nmol/l (IQR: 26.3–56.1) after statin intake ($P=0.828$).
Conclusion
Long-term high dose atorvastatin treatment in patients with type 2 diabetes mellitus did not affect serum vitamin D levels and calcium homeostasis.

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EP56

What is the diagnostic serum ACTH threshold in adrenal Cushing?

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Background
Diagnostic work-up for Cushing Syndrome (CS) can be challenging and is based on clinical and biochemical assessments. Once steroid excess is biochemically

confirmed, the diagnostic serum ACTH threshold for determining ACTH-independent Cushing is debatable. A threshold of less than 15 ng/l has been adopted in our regional guidelines.
Aims
To investigate serum ACTH levels in patients with proven adrenal Cushing and to assess the clinical utility of 24-hour UFC and urine steroid profiling (USP) in the work-up for CS.
Methods
All patients undergoing unilateral adrenalectomy from January 2019 to February 2022 at the RVI were included. Data extracted: demographics, preoperative biochemical assessment, radiological & histological findings, post-operative short Synacthen test (SST)
Results
27 patients had unilateral adrenalectomy for CS. F:M was 8:1 with a mean age of 59 years at diagnosis. 16 patients had a left-sided adrenal lesion, 10 had a right-sided one and 1 patient had bilateral lesions. Pre-operative random ACTH levels were <5, 5-9 and 10-12 in 56%, 37% and 7% of patients respectively. 22 patients had CS confirmed on either dynamic testing (20) or 24-hr UFC (1) or USP (1). The other 5 patients all failed their SST soon after surgery, thereby confirming previous adrenal Cushing. 24-hr UFC was elevated in only 36% of patients. USP was diagnostic in 25% of cases. Atrophy of the adrenal cortex was observed in 48% of resected adrenal glands. 3 patients passed their SST relatively soon post-surgery and histological examination in 2 out of these 3 cases demonstrated focally expanded or nodular adrenal cortex. 1 out of these 3 patients demonstrated ongoing steroid excess on biochemical retesting.
Conclusions
Majority of patients with adrenal Cushing have a random serum ACTH level of $<$ 10 ng/l. Pre-operative diagnostic yield from 24-hr UFC and USP is poor. Post-operative failed SST confirms prior ACTH-independent Cushing. For those patients who pass their SST soon after surgery, reassessment for steroid excess is warranted, especially if histology does not demonstrate atrophy of adrenal cortex.

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EP57

Adrenal venous sampling in patients with hyperaldosteronism

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Objective
Adrenal venous sampling (AVS) is a reliable procedure to differentiate if in patients with primary aldosteronism (PA) aldosterone production is unilateral or bilateral and guide treatment of these patients. Our objective was to describe their characteristics and the outcomes of the AVS.
Methods and patients
Observational longitudinal clinical study between July 2020 and November 2022 in patients who underwent AVS in our Hospital.
Results
21 patients included. 24 AVPs performed. Mean age: 56.1 ± 12.66 years. 52.4% women. Reason of PA screening: 38.1% resistant high blood pressure (HBP), 23.8% HBP and adrenal adenoma and 38.1% HPA and hypokalemia. 90.5% patients with an adenoma in the CT: 28.6% in the right gland, 57.1% in the left and 4.8% in both. 9.5% of patients without adenoma in CT. 70.8% of catheterization of both adrenal glands was successful.35.3% with no lateralization. Among the 11 successful AVS with lateralization, in 9 of them AVS lateralization matched the image. In 1 patient AVS lateralized to the opposite side. In 1 patient AVS showed left lateralization although no adenoma was seen in CT. 29.2% unsuccessful AVS: Most of them (85.7%) because of inadequate right adrenal vein catheterization.
Conclusion
– In spite of the limited number of AVS performed in our center, AVS is successful in most of the patients in our series. As previously described, inadequate right adrenal vein catheterization is the main cause of unsuccessful AVS.– In most patients AVS lateralization results matched the side of the adenoma in the CT image if it was present.

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EP58

Unusual "Square Wave" Presentation of Severe Prolonged Hypercortisolemic Followed by Eucortisolemic Phases in Patients with Cyclical Cushing Syndrome

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Background
Cyclical Cushing syndrome (CCS) is a rare variant of Cushing syndrome (CS) characterized by periodic cycles of cortisol excess. Diagnosis of CCS is difficult because cortisol excess occurs unpredictably and often limited to short periods. We present 2 unusual cases where the patients developed severe prolonged life-threatening "square wave" hypercortisolemic phase followed by eucortisolemia, both phases extending $>$ 3 months. Case 1: A 75 year old male presented with acute atrial fibrillation, 9 kg weight loss over 3 months, facial plethora, leg edema, muscle weakness, hypertension, hyperglycemia, hypokalemia of 2.6 mEq/l and had UFC 20 $\times$ ULN, ACTH 3 $\times$ ULN and 11 PM cortisol 66 μg/dl. High-dose dexamethasone did not suppress his cortisol, no gradient on IPSS, and CT chest/abdomen/pelvis and ^{68}Ga-DOTATATE PET/CT studies did not reveal an ACTH source. Due to his clinical deterioration, ketoconazole was started. After 3 weeks of treatment, cortisol deficiency developed and ketoconazole was stopped. For the following 3 months thereafter without ketoconazole, UFC, 8 AM cortisol and LNSCs remain normalized with resolution of majority of symptoms enabling the patient to gradually increase his physical activity. Case 2: A 61 year old female presented with 3 kg weight loss over 2 months, muscle weakness, edema, spinal compression fractures, uncontrolled hypertension and hyperglycemia, hypokalemia of 2.2 mEq/l, UFC 5 $\times$ ULN, 8 AM ACTH 2 $\times$ ULN and 11 PM cortisol 63.2 μg/dl. Due to her severe comorbidities, she was treated with IV etomidate followed by ketoconazole. No gradient was found on IPSS, and CT chest/abdomen/pelvis and ^{68}Ga-DOTATATE PET/CT studies failed to reveal an ACTH source. After 5 months, 8 AM ACTH, UFC, 8 AM cortisol and fasting glucose normalized. Because she had some side effects to ketoconazole, the drug was stopped after 2 months. After 4 months being off ketoconazole, UFC, cortisol, LNSCs and blood pressure remain normalized.
Discussion
These two cases highlight the importance of identifying and effectively treating severe prolonged "square wave" hypercortisolemic phase of CCS, and to closely monitor for eucortisolemia development. During the eucortisolemic phase, close monitoring is recommended for re-emergence of hypercortisolemia by self-checking glucose, blood pressure, weight and PM salivary cortisol assessments so that treatment can be promptly instituted if and when hypercortisolemia resurfaces. To our knowledge, severe prolonged "square wave" hypercortisolemia followed by eucortisolemia has not been reported in CCS. Herein, we describe a new variant of presentation of severe cortisol excess of this entity.

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EP59

Adrenocortical Oncocytoma: A bout 7 cases

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Introduction
Adrenal oncocytomas are rare and usually present as incidentally detected masses. The aim of this study is to evaluate the clinical characteristics of a series of patients with adrenal oncocytoma.
Material and Methods
we retrospectively collated all patients admitted to Bologhine Hospital between 2010 and 2020 for adrenal masses and who underwent surgery and a diagnosis of adrenal oncocytoma at the anathomo-pathological study ($n=07$). Demographic, clinical, secretory, radiological and pathological characteristics were evaluated.
Results
Of these 07 patients, 71.4% ($n=5$) were women and 28.6% ($n=3$) were men. They were between 27 and 49 years old ($37.7 \pm$). Four (57.1,%) of the masses were secretory. The masses had a mean length of 91 mm (70-130 mm). Three (42.9%) oncocytomas were classified as benign and the others as having uncertain malignant potential according to Lin-Weiss-Bisceglia criteria. The patients were followed for 36-96 months, no local recurrence and no distant metastasis were detected.
Conclusions
Because there are no clinical and imaging features to differentiate adrenal oncocytomas from other types of adrenal masses, they should be kept in mind in the differential diagnosis of adrenal masses, especially those of large size and those suspected of being adrenal carcinoma.

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EP60

A pheochromocytoma revealing a neurofibromatosis type 1: A case report

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Introduction
Neurofibromatosis type 1(NF1) is an autosomal dominant genodermatosis that affect multiple organs. It represents one of the most frequent genetic diseases. The diagnosis is primarily clinical and is based on the NIH criteria (National Institutes of Health) established in 1988,and revised in 2021. We report a case of male patient with NF1 revealed by a pheochromocytoma.
Case Report
A 26-years-old man patient with no previous medical history, who presented at the age of 6 the appearance of coffee-like spots, neurofibromas and diffuse lentigines. The evolution was marked by abdominal pain more accentuated in the right hypochondrium. Abdominal CT scan showed a well-limited adrenal tissue mass $50\times57\times40$ mm, with tissue density (49 units in C-). Plasmatic metanephrines were elevated. The eye fundus showed Lich nodules. Brain MRI showed an unidentified bright object related to his disease. Right Surrenalectomy was performed after medical preparation with doxasocin. Histopathological study reveled an agressive pheochromocytoma.
Discussion
NF1 is a disease with heterogeneous clinical expression. On the clinical level, it presents a polymorphic profil, with coffee-like spots, plexiform neurofibromas, axillary and/or inguinal lentigines, Lich nodules, subcutaneous and cutaneous neurofibromas. Pheochromocytoma is a rare disease in NF1, affecting 1 to 15% of NF1 patients, according to studies, This diagnosis must be suspected in a subject with NF1 subject in front of clinical signs of hypertensive flare-ups (sweat flare-ups, palpitations, headaches, anxiety, agitation); minor signs such as malaise, weight loss, abdominal or lumbar pain are also possible. The diagnosis of pheochromocytoma is based on plasma and/or urine metanephrines and on abdominal imaging as in the case of our patient. Screening is recommended every 5 years from the age of 35.
Conclusion
NF1 is a disease with heterogeneous clinical expression: some NF1 carriers present an uncomplicated profil; but others develop rare complications that can affect every system of the human body, such as pheochromocytoma which is one of these complications.

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EP61

Pheochromocytomas, a series of 68 cases

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Introduction
Pheochromocytoma is a rare endocrinopathy, most often benign. Early and multidisciplinary management of this disease allows to avoid its dreadful complications.
Objective
To describe the epidemiological, clinical and biological characteristics of patients with pheochromocytoma.
Patients and Methods
Retro-prospective descriptive study, including patients hospitalized in the Endocrinology Department of CHU Ibn Rochd of Casablanca from 1996 to 2022. Data analysis was done by SPSS software.
Results
The mean age was 47.3 years, the sex ratio was 1.07. The main symptom was hypertension followed by Menard's triad. Cardiac and/or renal complications were found in 29% of patients. The location of the tumor was adrenal in the majority of cases (94%). The management was essentially surgical preceded by a medical preparation. A delay in diagnosis with an incidental finding was found in 28%. The anatomo-pathology was benign in the majority of cases with 7 cases of malignant pheochromocytoma. Death was recorded in 7 patients.
Conclusion
Pheochromocytoma is a rare and often benign endocrinopathy. Our work shows the delay of the diagnosis at the stage of complications of this pathology.

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EP62

Consanguineous marriage and 5 triple a syndrome

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Aim
Triple-A Syndrome (TAS) is a rare autosomal recessive disorder characterized by three cardinal symptoms: alacrimia, achalasia and adrenal insufficiency due to ACTH insensitivity. The disease is caused by mutation in the AAAS gene on chromosome 12q13. Mutations in AAAS were identified in more than 90% of individuals and families with TAS. The aim of this study is to discuss the clinical, laboratory and molecular genetic analysis results of 5 patients with TAS.
Materials and Methods
Five triple A syndrome patients from the same family who were genetically diagnosed were included in our study. Clinical, laboratory and genetic findings of the patients between 2018-2022 were obtained retrospectively.
Results
All of the patients were Syrians and relatives, 3 of them were siblings from the same family and 2 of them were cousins. The first admission of all patients was with achalasia findings. Esophagosgastromyotomy (dor funduplication) was performed in three patients and esophageal balloon dilatation was performed in 2 patients due to dysphagia. The first diagnosis of triple A syndrome(TAS) was made when she applied to the emergency room with dysphagia, nausea and vomiting and was examined in the intensive care unit, while achalasia was diagnosed and the diagnosis was made when she entered adrenal crisis in the follow-up. Then, people with similar symptoms in the family were examined and a total of 5 patients were diagnosed with TAS. All patients had alacrima, adrenal insufficiency and achalasia diagnoses. In addition, 2 had hyperreflexia, 4 had learning difficulties, 4 had hypernasal speech, 3 had muscle weakness, 3 had delayed speech, 2 had excessive sweating, 3 had thenar/hypothenar atrophy, and 3 had short stature. In all patients, AAAS gene was sequenced with sanger sequencing and c.1432C>T (p.Arg478*) mutation was detected in both alleles (homozygous).
Conclusion
Diagnosis of adrenal insufficiency is of vital importance in both the diagnostic and therapeutic stages of achalasia while examining and treating achalasia. Although these two diseases seem to be two different entities, the fact that they were detected in one patient at the same time is important in terms of recognizing and treating the neurological and other findings of triple A syndrome, especially alacrima. At the same time, it increases the incidence of genetic diseases in societies where consanguineous marriages are common. Therefore, the prevalence of consanguineous marriages in some regions of Syria and Turkey, diagnosis and treatment of genetic diseases are of particular importance.

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EP63

Adrenocortical vascular network and hormonal output after daidzein application in a rat model of the mild andropause

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Soy isoflavone daidzein exerts some beneficial effects in different ageing-related, chronic diseases and may represent a promising alternative to classical estrogenization of the prostate cancer suffering subjects. The aim of this study was to examine the effects of daidzein on the adrenocortical vascular network and hormonal output in a rat model of the mild andropause. Adult (3 months old) Wistar rats were divided into sham-operated (**SO**; $n=7$), orchidectomized (**Orx**; $n=7$) and daidzein treated orchidectomized (**Orx+D**; $n=7$) groups. Daidzein (30 mg/kg b.m./day) was administered subcutaneously for three weeks, while the **SO** and **Orx** groups received the vehicle alone. Adrenocortical vascular network properties were identified using Novelli histochemical staining, vascular endothelial growth factor (VEGF) immunostaining and the newCast stereological

software. Blood concentrations of aldosterone, corticosterone and DHEAS were measured by immunoassays. Volume densities of blood vessels and VEGF depots within the adrenal cortex were not significantly changed after daidzein treatment, although there was a tendency of decrease of these parameters. On the other hand, daidzein application increased ($P<0.05$) blood concentration of aldosterone by more than 2.5 times and 41%, in comparison with the same parameter in sham-operated and orchidectomized group, respectively. Corticosterone concentration in daidzein-treated, orchidectomized rats showed a tendency of elevation ($P>0.05$) compared to the both **SO** animals and orchidectomy alone. DHEAS blood concentration after daidzein application remained at the level of the **Orx** group, which in both cases ment elevation ($P<0.05$) by around 80% in comparison with the same parameter in **SO** group. We conclude that daidzein significantly increases aldosterone and to some lower extent corticosterone output in a rat model of the mild andropause, without significant rearrangements of the entire adrenal cortex vascular network.

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EP64

Cushing's Syndrome due Primary bilateral macronodular adrenal hyperplasia–a case series from a tertiary hospital

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Primary bilateral macronodular adrenal hyperplasia (PBMAH) is a rare cause of Cushing's syndrome (CS). It is a highly heterogeneous disease with multiple adrenal macronodules and variable levels of cortisol excess. The pathogenesis is complex and different mechanisms such as aberrant hormone receptors, local production of ACTH in adrenal tissues and genetic mutations have been identified. The approach is not well established. Nine patients with PBMAH who are currently followed in our department were identified. Six of them were females and the median age at diagnosis was 49.0 (range 33-64) years. All patients were investigated as a result of adrenal incidentalomas, with the exception of one patient that was studied for overt CS. At the time of diagnosis, two patients did not have clinical manifestations of CS. The most frequent signs were abdominal obesity (4/7), ecchymosis (3/7) and moon face (3/7). Median BMI was 28.2 (range 24.3–32.3) kg/m^2. All patients had hypertension, eight had dyslipidemia and seven had abnormal glycaemic metabolism (diabetes (3/7) and prediabetes (4/7)). Two cases had hypokalaemia (3.10 mEq/l). Median morning plasma cortisol after 1 mg dexamethasone overnight suppression test was 22.2 (range 1.60–27.60) µg/dl and median cortisol after low-dose dexamethasone suppression test (2 mg/day for 48 hours) was 14.4 (range 1.10-24.4) µg/dl. Median 24-h urinary free cortisol was 200.7 (range 59.4–520.1) µg/24 h [1.48 (range 0.34–3.80)-fold ULN]. Median late-night salivary cortisol was 0.73 (range 0.64–2.70) µg/dl [2.20 (range 2.00–8.13)-fold ULN]. Mean matinal ACTH level was 1.83 ± 1.58 pg/ml and median DHEAS was 17.6 (range 3.8–90.0) µg/dl [ref. 35.4-256]. Primary aldosteronism had been diagnosed in one patient (aldosterone-to-renin ratio 7.26 ng/µg). Only one case had several nodules on one adrenal with an apparently normal contralateral gland. Median largest nodule size was 30.5 (range 20.0–39.0) mm. In two of four patients had found pathogenic mutations in the ARMC5 gene. Seven patients were screened for aberrant receptors: in three cases all tests were negative; in four patients had at least one test with a partial response (glucagon test was the most frequently positive). Seven patients underwent unilateral adrenalectomy. However, only two remain free of hypercortisolism (median follow-up 4.2 y). One patient underwent unilateral adrenalectomy recently. Two patients are under annual active surveillance and their comorbidities are controlled (median follow-up 7.5 y). PBMAH is a heterogeneous and challenging disease in terms of treatment. Unilateral adrenalectomy may be an option. However, patients are rarely free of hypercortisolism and require monitoring and management of comorbidities.

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EP65

Bilateral primary aldosteronism prediction by Integer scoring system

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Background
Adrenal venous sampling (AVS) is the gold standard to differentiate patients with unilateral primary aldosteronism (UPA) from those with bilateral disease (BPA). As this is an invasive method, there are a lot of different scoring systems developed for primary aldosteronism (PA) subtyping. Integer scoring system is one of those established for BPA subtyping.
Objective
The aim of this study was to evaluate the efficiency of using the online Integer scoring system in predicting BPA, as a possible surrogate for AVS.
Methods
We performed a retrospective analysis of 105 patients (66 female, median age at diagnosis 53 years (20-75)) treated for PA in our center between 2015 and 2022. AVS was bilaterally successful in 86 (82%) patients. According to AVS, 52 (60%) patients were diagnosed as UPA and 34 (40%) as BPA. The Integer score was calculated based on serum potassium level (<3.9 mmol/l - four points, 3.5-3.9 mmol/l - three points), sex (female sex - one point), imaging finding on CT (absence of nodules during computed tomography - three points), baseline plasma aldosterone concentration (<210 pg/ml - two points) and baseline aldosterone to renin ratio (<620 - two points). The result above 8 was considered as predictive for BPA.
Results
Of 34 patients diagnosed with BPA using the AVS, the Integer score was diagnostic in 9 of them, giving a positive predictive value of 26%. The negative predictive value was 96%, sensitivity 82% and specificity 67%.The median score for BPA subtyping in our patients was 4 with a range from 3.5 to 6.
Conclusion
Our results suggest that Integer scoring system is not applicable for PA subtype prediction in our center and that each center should determine their own score. To the extent that each center does not have a scoring system, AVS remains the only diagnostic method for subtyping PA.

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EP66

Overview and factors that impact quality of life in patients with Cushing's syndrome

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Background
Quality of life (QoL) has become a useful outcome in recent studies among different specialties. In Cushing's syndrome, elevated cortisol levels result in a decreased QoL, the cause for this impairment being multifactorial. More studies are necessary to find modifiable factors where doctors could intervene and thus improve QoL.
Objective
To evaluate QoL in a group of Romanian patients with Cushing's syndrome. Design: We performed a cross-sectional study, administering three standardized questionnaires (EuroQol-5D, CushingQol and a recently developed one, specific for Cushing's disease, QoL-CD) to 24 patients (mean age 52.46 ± 11.39 years) with both Cushing's disease ($n=16$) and syndrome ($n=8$). The questionnaires were administered by telephone in march 2022.
Results
There was no difference between the two aetiologies when evaluating gender, age, body mass index, serum cortisol at diagnosis and remission status. The most affected domain was the one referring to pain/discomfort, where 66.7% patients reported problems. Mobility was the second most affected dimension (41.7%), followed by anxiety/depression and usual activities (each 37.5%). The least impaired domain was self-care. Patients with Cushing's syndrome reported a significantly higher degree of impairment in almost all of the investigated domains compared to the healthy Romanian population: mobility (41.7 vs 17.22, $P=0.0047$), pain/discomfort (66.7 vs 26.99, $P=0.0001$), usual activities (37.5 vs 15.81, $P=0.009$) and anxiety/depression (37.5 vs 17.22, $P=0.0249$). Patients with obesity reported lower QoL in the psychosocial subscale (51.16 vs 69.72, $P=0.048$) of the CushingQol questionnaire, but not in the physical one, compared with those without obesity. The presence of depression (31.25 vs 65.75, $P<0.001$) and anxiety disorder (27.78 vs 62.50, $P=0.012$) was associated with lower scores. Other conditions, such as cardiac ischemic disease and dyslipidaemia, were also associated with poor QoL. Remission status did not influence any of these scores. In the QoL-CD questionnaire, patients with diabetes reported impairment in domains concerning mental status ($P=0.020$) and general health ($P=0.043$). Depressive disorder was linked with problems in general health and emotional health domains. The overall scores from this questionnaire were

negatively correlated with those of the CushingQol questionnaire (rho = -0.874, $P < 0.001$). The same correlation was found when analysing related domains such as emotional health and the psychosocial subscale from the CushingQol (rho = -0.710, $P = 0.002$).

Conclusions

Improving the control of conditions such as obesity, diabetes and psychiatric disorders could result in better QoL for these patients. The use of QoL-CD is feasible and helpful in real clinical setting.

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EP67

Effect of glucocorticoid replacement dose on bone mineral density in patients with Addison disease: A cross-sectional Tunisian-based study

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Introduction

Addison disease (AD) is associated with high risk of decreased bone mineral density (BMD) and osteoporosis. Causes are complex, including lifelong glucocorticoid replacement therapy. Several studies have pointed a significant relationship between glucocorticoid dose and low BMD in patients with AD. The aim of our study is to assess the impact of glucocorticoid replacement dose on BMD among Tunisian patients with AD.

Patients and Methods

We conducted a descriptive and analytical cross- sectional study that included 50 patients with AD taking glucocorticoid replacement therapy for at least 5 years and followed at the Endocrinology department of Hedi Chaker University hospital, Sfax,Tunisia, from March 2020 to July 2021. BMD was evaluated using dual-energy X-ray absorptiometry (DEXA), at the lumbar spine (L1-L4) and femoral neck sites. The relationship between glucocorticoid dose and BMD was assessed.

Results

Patients had a mean age of 49.5 ± 13.9 years (18-78 years) and a disease duration with a mean of 13.9 ± 8.7 years (5-35 years) and 80% were women. None of the participants reported having spontaneous or traumatic fracture. All patients were treated from diagnosis with hydrocortisone (HC), distributed in two daily doses in 67% of patients. Twelve percent of patients received fludrocortisone as mineralocorticoid replacement. Average daily HC dose at the time of AD diagnosis was 25.7 ± 9.1 mg (15-50 mg) corresponding to 0.47 ± 0.21 mg/kg (0.18-1.08 mg/kg) and an average daily dose adjusted for body surface area of 16.29 ± 7.54 mg/m^2 (15.6-37.94 mg/m^2). During follow-up, the average daily HC dose was 27.4 ± 6.7 mg (15-42.1 mg) corresponding to 0.388 ± 0.128 mg/kg (range, 0.175-0.711 mg/kg) and a mean dose per body surface area of 14.836 ± 4.658 mg/m^2 (7.486-31.460 mg/m^2). Mean cumulative hydrocortisone dose was 374.636 ± 283.821 mg (60–1184, 94 mg). Low BMD (less than 2 standard deviations [SD] of the mean value of an age-matched reference population) was depicted in almost half of patients (48%). Twelve (24%) patients had osteoporosis. As well, osteopenia was recorded in 24% of patients. Patients with osteoporosis were older ($P = 0.018$) receiving higher mean daily dose than normal BMD ((26.5 ± 8.3 mg/day vs 25.6 ± 6.3 mg/day, $P = 0.9$). Mean cumulative HC dose was higher in patients with osteopenia/osteoporosis than those with normal osteodensitometry but without significant correlation (462.2 ± 373.2 mg vs 344.6 ± 245.5 mg, $P = 0.48$).

Discussion

Glucocorticoid replacement therapy during AD is associated with low BMD requiring better therapeutic adjustment of HC doses.

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EP68

Health state utility value of Cushing syndrome patients after bilateral adrenalectomy–systematic literature review and mapping to EQ-5D

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Background

Bilateral adrenalectomy (BLA) is a treatment option for patients suffering from endogenous Cushing syndrome (CS). It consists of the surgical removal of both adrenal glands. Even though BLA offers immediate control of cortisol excess, given the risk of adrenal insufficiency, it requires life-long glucocorticoid and mineral corticoid replacement. It may lead to perioperative and long-term complications which affect patients' quality of life (QoL). Health state utility values are essential parameters in cost-effectiveness models and should be established with a systematic literature review (SLR). The generic EQ-5D is the preferred QoL instrument by health technology assessment bodies.

Objectives

The main objective of the SLR was to identify relevant utility data of adult patients with endogenous CS after BLA to enable performing cost-effectiveness estimation in this therapeutic area. Another goal was to provide clinicians and researchers with a better understanding of the impact of BLA on patients' QoL.

Methods

The search was conducted using electronic databases, Embase® and MEDLINE. Eligibility criteria were based on the population, interventions, comparators, and outcomes (PICO) framework. The search terms included EQ-5D, other recommended measures like HUI 1-3, SF-6D, SF-36 and other instruments which, if no relevant EQ-5D data were available, could be mapped onto EQ-5D. The quality of full-text publications was assessed using a validated checklist provided in the literature.

Results

Out of 146 records identified, 5 unique studies were eligible for inclusion. Four studies assessed the QoL of CS patients after BLA using SF-36 and one using SF-12. All included studies demonstrate consistently that CS patients after BLA had lower QoL scores compared to the general population. The most impaired domains of SF-36 were bodily pain, general health, vitality and social functioning. Both physical and mental composite score of SF-12 were deteriorated. As no EQ-5D values were identified, SF-36 and SF-12 outcomes were mapped to EQ-5D-3L using published and validated regression models. EQ-5D values as estimated for different mapping models were oscillating between 0.5 and 0.7, with median value equal to 0.65. Reference population norms for EQ-5D-3L values, matched to CS patients by age, ranged from 0.85 to 0.97, depending on the country of origin.

Conclusions

Despite control of CS, CS patients after BLA have impaired QoL. The utility value of their health state, mapping SF-36 and SF-12 results to EQ-5D, is approximately 0.65. This relatively low value may be attributable to comorbidities, especially adrenal insufficiency.

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EP69

Effects of Osilodrostat and Metyrapone on steroidogenesis in adrenocortical H295R tumor cells in vitro

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Introduction

Osilodrostat and Metyrapone are two CYP11B1 inhibitors used for the treatment of patients with Cushing syndrome. Despite their common suspected mechanism of action, the comparison of serum steroid profiles determined in HPLC-MS/MS in patients treated by either Osilodrostat or Metyrapone for an ACTH-dependent Cushing syndrome identified higher levels of 11-deoxycortisol and androgens in patients treated by Metyrapone than in those treated by Osilodrostat (*F. Bonnet-Serrano and al., EJE, 2022*). This suggested a potential inhibitory effect of Osilodrostat on other steroidogenic enzymes than CYP11B1. The objective of this study was to understand the mechanisms underlying the differences observed in treated patients in clinical routine by comparing the effect of both drugs on the steroid secretion profile of adrenocortical carcinoma cells *in vitro*, exposed to either Osilodrostat or Metyrapone.

Methods

H295R cells were incubated for 72 hours with five different concentrations of Osilodrostat or Metyrapone (0.05 µM, 0.1 µM, 0.5 µM, 1 µM and 5 µM). A profile of ten steroids was measured in the supernatant using HPLC-MS/MS analysis. Cell viability after drug exposure was evaluated by Crystal Violet assay.

Results

Half-decrease in cortisol and corticosterone levels was observed with only 0.05 µM of Osilodrostat (from 270 to 114 nmol/l and from 12.9 to 4.0 nmol/l,

respectively) vs 0.5 μM of Metyrapone (from 267 to 118 nmol/l and from 11.9 to 5.6 nmol/l, respectively). These inhibitions also induced an increase in upstream steroids, 11-deoxycortisol and 11-deoxycorticosterone. Thus, Osilodrostat had a higher inhibitory effect on CYP11B1 and CYP11B2 than Metyrapone, as suggested by the higher 11-deoxycortisol/cortisol and 11-deoxycorticosterone/-corticosterone ratios, respectively. Androstenedione levels showed a slight increase $\leq$20% with Osilodrostat while no variation was observed with Metyrapone. The same experiment and analysis will be performed using different concentrations and exposure durations to better characterize the effect of both drugs on steroid precursors and androgens pathway.

Conclusion

Osilodrostat induced a stronger inhibition of CYP11B1 and CYP11B2 activities than Metyrapone in H295R cells, resulting in a higher decrease in cortisol and corticosterone levels. The comparison of the steroid profile and the expression of steroidogenic enzymes in basal and treated conditions should also give us interesting insights in the action of these drugs on adrenocortical cells. This study would therefore, help to better understand the molecular cause of the adverse effect observed in treated patients, especially hyperandrogenism.

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EP70

Glycerophospholipid circadian profiles in serum and dried blood spot in healthy subjects

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Introduction

Lipidomics is an emerging approach to characterize circadian rhythm alterations due to diseases of the hypothalamus-pituitary-adrenal axis. Glycerophospholipids are membrane structural constituents and key players in cell signalling, homeostasis and inflammatory and immune responses. Among blood derivatives, serum may reflect the soluble fraction, whereas dried blood spot (DBS) may reflect the cell membrane fraction of these lipids. However, little information is available about individual glycerophospholipid distribution among different blood derivatives as well as about their circadian fluctuation.

Aim

To compare glycerophospholipid levels and their variation during the daytime as assessed in serum and DBS.

Methods

Six normal-weight healthy adults (3 males, 3 females) aged 26-50 y were enrolled. For 7 days, ending with the observation day, subjects had a Mediterranean diet standardized in composition and time. Subjects underwent six paired venepunctures and finger-pricks to obtain serum and DBS, respectively, at pre-established times: 30 min before and 2 hours after breakfast (7.30), lunch (13.30) and dinner (19.30). Ninety glycerophospholipids were quantified by flow injection - tandem mass spectrometry.

Results

Eighty-four metabolites were detected both in serum (mean minimum concentration: 0.117 μM, phosphatidylcholine-diacyl (PC-aa)-C24:0; mean maximum concentration: 413.7 μM, PC-aa-C34:2) and DBS (mean minimum concentration: 0.284 μM, PC-acyl-alkyl(ae)-C44:3; mean max concentration: 218.6 μM, PC-aa-C34:2). Among these, 41 analytes were higher and 35 lower in basal serum vs DBS (P: $<$0.001-0.046). Further 1 and 4 metabolites were only detected in serum and DBS (mean range concentration: 0.746-2.40 μM), respectively; 1 was not detectable. Levels of 75 glycerophospholipids significantly correlated between DBS and serum (P: $<$0.0001-0.040). Highest correlations were found for PC-aa-C34:4 (r=0.933), PC-aa-C32:2 (r=0.912) and PC-aa-C34:3 (r=0.909). Significant variations along the six time points were observed for serum PC-ae-C32:1, lysoPC-a-C16:0, lysoPC-a-C16:1, lysoPC-a-C17:0, lysoPC-a-C18:1, lysoPC-a-C18:2, lysoPC-a-C20:3 and lysoPC-a-C20:4 (P: $<$0.001-0.031), showing a positive linear or quadratic trend. The latter three compounds showed a parallel fluctuation in DBS (P: 0.001-0.014). Forty-six other glycerophospholipids showed significant variations in DBS along the six time points (P: $<$0.001-0.049), mostly with negative linear trend. Strongest variations were found for PC-aa-C24:0, PC-ae-C30:0, PC-ae-C36:0, PC-ae-C38:0, PC-ae-C38:1 and lysoPC-a-C26:0 (all P: $<$0.001).

Conclusions

In our healthy cohort, significant differences in serum and DBS glycerophospholipid levels were observed. DBS displayed daily variations of a much larger panel of glycerophospholipids than serum. This is consistent with the presence of the cellular fraction in DBS. DBS may therefore represent a convenient and more informative tool to study glycerophospholipid involvement in diseases related to circadian rhythm imbalance.

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EP71

Small Cell Neuroendocrine Carcinoma of the Larynx: A Case Report

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We report a case of small cell neuroendocrine carcinoma of laryngeal localization. The involvement of the larynx still exceptional. We present in this paper the radiological, pathological and therapeutic aspects of this tumor that was diagnosed in a 48-year-old man. A 59 years old male patient, chronic smoker, with 10 packs per year; without any particular medical history. he consulted for a rapidly progressive cervical swelling since one year, associated with dysphonia. The whole evolving in a context of apyrexia and alteration of the general state (asthenia, weight loss considered very important not quantified with a preserved appetite).There was no dysphagia, no dyspnea, no carcinoid syndrome or other paraneoplastic syndromes. The patient consulted an ear nose and throat physician, who ordered a cervicothoracic computed tomography showing thickening of the right vocal chord with two nodular lesions measuring 8$\times$10 mm for the largest one, with multiple cervical ADPs visible in the jugulocarotid artery, measuring 23 mm on the right and 15 mm on the left, with necrotic content. Rigid laryngoscopy under sedation revealed a regular submucosal thickening of the right vocal cord extending superiorly. With presence of jugulo-carotid adenopathies. The anatomopathological study of the biopsy showed: an undifferentiated carcinoma, largely necrotic, infiltrating the fibrous tissue with vascular emboli at the level of the labelled specimen. A second specimen of the right vocal cord discreetly reworked by fibrosis without neoplastic localization at this level is associated. This morphological aspect must make us eliminate an aerodigestive primary. With immunohistochemical complement morphological aspect and immunohistochemical profile in favor of an infiltrating small cell neuroendocrine carcinoma (anti AE1/AE3: diffuse positivity/anti chromogranin A: diffuse and intense positivity/anti synaptophysin: diffuse positivity of moderate intensity/anti -KI67: estimated at 60%). Complementary tests showed a very high carcinoembryonic antigen level of 156.4 ng/ml, i.e. 26 times normal. The tumor extension assessement showed secondary iliac osseous lesions. The octreoscan was not performed due to lack of reagent. Given the histological nature of the tumor which contraindicates surgical treatment, the case was discussed with the oncologists with the decision to stop the investigations and to refer the patient for urgent radio-chemotherapy.Keywords: larynx, small cell neuroendocrine tumor, endoscopy, radiology, pathology, treatment.

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EP72

Characteristics of Hypertension in patients with pheochromocytomas

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Introduction

Pheochromocytomas are rare catecholamine-secreting tumors presenting with various clinical manifestations. Hypertension is the most common finding in pheochromocytomas. It can be either persistent or paroxysmal. Study Design: We conducted a retrospective study of 34 patients who were admitted into the endocrinology department of Charles Nicolle hospital, with a diagnosis of a pheochromocytoma from January 2005 to November 2022.

Results

Twenty one patients (64%) had a family history of hypertension. Nine patients (27%) had diabetes and eight patients (25%) had dyslipidemia. Twenty six patients (77%) had hypertension. The median of years with hypertension was 3.5 years IQR (1-5,7). The mean number of used antihypertensive drugs was 2.4 $\pm$ 1.3 [extremes:1-6]. Two patients had coronary disease and one patient had heart failure. An ultrasound myocardium imaging was practiced in 22 patients. Myocardial amyotrophy was detected in 36% of cases (eight patients). Five patients had electric EKG abnormalities. Hypertensive retinopathy, microalbuminuria and chronic kidney disease were detected in 18, 93 and 20% of cases, respectively. Surgical treatment was performed in 27 cases (93%). Fifteen (56%) patients were cured of their hypertension after surgery.

Conclusions

Pheochromocytomas are considered as one of the most common causes of curable hypertension. Early diagnosis of theses tumors is important, owing the possibility of curing hypertension and preventing its lethal complications.

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EP73

«Non-classical» pheochromocytoma, clinical case

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Neuroendocrine neoplasias (NENs) are a heterogeneous group of tumors that differ in appearance, growth patterns, and clinical symptoms and develop from neuroendocrine cells and, accordingly, unusually similar cytological characteristics. Pheochromocytoma is considered as not epithelial type of NENs. We would like to present a clinical case of pheochromocytoma with difficulties in laboratory diagnosis and morphological verification. Female patient P., 60 years old, for 10 years, she was observed by a cardiologist with arterial hypertension (Grade 3) and chronic heart failure (NYHA Clase III), antihypertensive therapy with 3 standard preparations has been repeatedly adjusted without sufficient clinical response. On treatment, patient had blood pressure up to 200/100 mm Hg accompanied by sweating, episodes of flushes of heat to the face. CT of the abdominal organs incidentally detected a left adrenal tumor size 46×41×45 mm (native density +14+52 HU). Daily urine: normetanephrine 471 mg/day (30–440), metanephrine 60 mg/day (30–440); chromogranin A 23.6 nmol/l (0.54–3). Laparoscopic left adrenalectomy was performed. According to the histological examination of the adrenal tumor, predominantly formed from the structure of a solid and alveolar with the presence of an angiomatous component of large cystic dilated vessels, from small monomorphic tumors cells with a narrow cytoplasm and a rounded nucleus, which in structure most of all resemble the structure of neuroendocrine tumors of the small intestine, "typical carcinoids". The minor component of the structure, characteristic of "classical" pheochromocytomas, was formed from alveolar structures from larger cells with abundant light cytoplasm, with nuclear and cellular polymorphism. When a tumor is detected, invasion of vessels into the tumor and local invasion of capsules. Considering the fact that the tumor has a non-specific structure for pheochromocytes, differential diagnosis was carried out between pheochromocytoma and metastases of intestinal NET or other localizations. Immunohistochemical detection of chromogranin A expression foci, a higher density in areas of a “typical” pheochromocytoma, as well as synaptophysin and CD56, revealed focal uneven expression of vimentin, as well as focal serotonin expression mainly in areas of a “carcinoid structure”. There is no expression of pan-cytokeratin, TFF-1, CDX-2. The average Ki67 2-8% (max 11%).

Conclusion

Pheochromocytoma of the adrenal gland "carcinoid-like" structure. After operation, the patient noted the normalization of blood pressure without preparations. This clinical case demonstrates the diversity of the clinical course and histological picture. Based on this, to establish an accurate diagnosis, we need detailed approach with a mandatory Immunohistochemical study to determine further tactics of treatment and monitoring.

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EP74

Malignant pheochromocytoma : A therapeutic challenge !

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Introduction

Pheochromocytomas are rare catecholamine-producing neuroendocrine tumors that are usually benign, but which may also present as or develop into a malignancy. Predicting such behavior is notoriously difficult and there are currently no curative treatments for malignant tumors.

Case Report

A male patient aged 23 years old who was investigated for headaches, flushing and palpitations. The patient presented with classic clinical features of NF-1, *café-au-lait* spots and skin nodules. Laboratory tests revealed elevated catecholamine levels in the 24-h urine collection. Computed Tomography Scan revealed a mass measuring 10×8.2×9.4 cm in the left adrenal gland and pulmonary metastases. He was operated on and histological examination confirmed the diagnosis of pheochromocytoma with a Pass score of 9. After surgery, urinary catecholamines were high and there were diffuse pulmonary and liver asymptomatic metastases in Octreotide scan uptake. The I131 MIBG scan revealed the progression of pulmonary and liver metastases and revealed bone metastases. Radionuclide treatment with use of 131-I MIBG is indicated.

Discussion

Pheochromocytomas are tumors of the adrenal medulla and extra-adrenal chromaffin tissue that secrete catecholamines, resulting in hypertension, whether sustained or paroxysmal, and other symptoms of increased production of catecholamines. They may be classified as sporadic or familial. Most of the pheochromocytomas are sporadic. Familial predisposition is seen mainly in patients with multiple endocrine neoplasia type 2, neurofibromatosis Type 1 (NF-1), von Hippel-Lindau disease and familial carotid body tumors .laparoscopic adrenalectomy (LA) has gained field in the surgery of the adrenals and nowadays it is the procedure of choice. A long-term follow-up is required to monitor for recurrence in patients with genetic predisposition. I-131 MIBG therapy has been widely used for metastatic or unresectable MIBG-avid pheochromocytomas and paragangliomas. Several groups have tried single or repeated therapy with a variable dose of I-131 MIBG.

Conclusion

The association of a malignant pheochromocytoma with neurofibromatosis type 1 although very rare should be known as pheochromocytoma and its metastases may be totally asymptomatic as in the presented case.

Keywords: Pheochromocytoma, metastasis-treatment
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EP75

Abstract withdrawn

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EP76

Impact of long-term atorvastatin use on renal function in type 2 diabetes patients

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Introduction

Statins are widely used in primary and secondary cardiovascular prevention. They have been described to improve renal function. We aimed in this study to evaluate the effect of high dose atorvastatin therapy on renal outcome in type 2 diabetes patients.

Methods

This was a single-center, prospective study, including 60 men with type 2 diabetes mellitus, aged between 40 and 65 years, statin-free, in whom the indication of a high dose statin treatment was indicated. Renal clearance was higher than 60 ml/mn/1.73 m^2 in all patients. The patients had two visits, before and six months after the daily intake of 40 mg of atorvastatin. During each visit, they underwent a clinical examination and a fasting blood sample was collected for biological measurements including creatinine.

Results

The median age was 58 years (IQR:52-62). The median duration of diabetes was 81 months (IQR: 26-132). Thirty-one patients (52%) had hypertension. The median weight was 86.5 kg (IQR: 78-94). Twenty-seven patients (45%) had a diabetic nephropathy; a microalbuminuria in 23 cases (38%) and a macroproteinuria in 4 cases (7%). Glomerular filtration rate (GFR) was between 60 and 89 ml/mn/1.73 m^2 in 16 patients (27%) before and 12 (20%) after statin use while GFR $\geq$ 90 ml/mn/1.73 m2 was observed in 44 (73%) before and in 48 (80%) after atorvastatin treatment. Serum creatinine levels decreased significantly from 74.5 µmol/l (IQR: 69.8-82.5) to 70.8 µmol/l (IQR: 64.9-78.3) ($P=0.001$). Creatinine clearance increased significantly from 100 ml/mn/1.73 m^2 (IQR: 88-110) to 105 ml/mn/1.73 m^2 (IQR: 93- 120) after atorvastatin therapy ($P=0.001$).

Conclusion

Long-term high-dose atorvastatin use improved renal function in type 2 diabetes patients.

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EP77

VCAM-1 concentration in patients 6 months after SARS-Cov2 infection

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Objectives
The excessive production of pro-inflammatory cytokines has been previously reported in the severe form of COVID-19. The cytokine storm is responsible for the induction of an inflammatory endothelial cell phenotype which is associated with the shedding of adhesion molecules. VCAM-1 is an endothelial adhesion protein that belongs to the immunoglobulin superfamily. Pro-inflammatory cytokines lead to the induction of VCAM-1 in the endothelium of blood vessels which is crucial for the recruitment, adhesion, and migration of leukocytes. The level of the soluble form of VCAM-1 (sVCAM-1) was shown to be increased in patients with severe COVID-19 and was associated with disease progression and mortality.
Aim
To assess VCAM-1 concentration in patients 6 months after the mild SARS-Cov2 infection (without hospitalization) in comparison to the control group as well as biochemical, hormonal, and anthropometric parameters, considering the influence of sex.
Material and Methods
The study group included 53 patients with a history of COVID-19 and 87 healthy subjects in the control group. Anthropometric parameters were measured. VCAM-1 concentration as well as hormonal (testosterone, insulin, morning cortisol) and biochemical parameters (glucose, alanine transferase, asparagine transferase, lipids) were measured.
Results
The statistically higher VCAM-1 concentrations were observed in the control group in comparison to the COVID-19 group (830, 342 ng/ml vs 772, 509 ng/ml, $P=0.03$). No statistically significant differences in C-reactive protein concentrations were observed between the groups. Significant positive correlations were observed between VCAM-1 and alanine and aspartate aminotransferases as well as with HDL-concertation in the COVID-19 group, although we did not observe significant differences in the concentration of aminotransferases and HDL cholesterol between both groups.
Conclusions
Based on the results of our study, it can be concluded that, at least 6 months after mild COVID-19 infection, there is no strong evidence of endothelial dysfunction in COVID-19 survivors. Surprisingly, we observed a significantly higher concentration of VCAM-1 in the apparently healthy control group.

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EP78

Primary bilateral macronodular adrenal hyperplasia: Is unilateral adrenalectomy enough?

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Introduction
Primary Bilateral Macronodular Adrenal Hyperplasia (PBMAH) represents $<2\%$ of causes of Cushing's Syndrome (CS). Clinical course is insidious, with adrenal bilateral macronodules and gradual cortisol excess, only rarely presenting with overt CS. The pathophysiology remains unclear, however, hyperactivation of the cAMP/PKA pathway, in 77-87% of cases through aberrantly expressed G-protein coupled receptors (GPCRs), has been described. Despite being a benign entity, PBMAH associated hypercortisolism may require aggressive management.
Objectives
To present a case of PBMAH diagnosed due to hypertension and overt CS, successfully treated with unilateral adrenalectomy.
Case Report
A 34-year-old woman presented with progressive weight gain, facial hair growth and headaches for 14 months. She had been diagnosed with prediabetes and hypertension, which motivated additional study. She had round plethoric face and hypertrichosis, dorsocervical and supraclavicular fat pads and easy bruising. Her weight was 66.5 kg with a body mass index of 24.4 kg/m^2. Laboratory evaluation showed a 9 am serum cortisol of 46.1 µg/dl (*n*:6.2-18), with circadian rhythm, as demonstrated by the measurement of salivary cortisol at 8 am and 11 pm; ACTH <1 pg/ml and 24 h urinary cortisol 6825 µg/24 h (*n*:124-581). Serum cortisol after 1 mg dexamethasone suppression test was 37.9 µg/dl, while salivary cortisol kept circadian rhythm. Androgen and mineralocorticoid hypersecretion were excluded. Adrenal CT scan documented evident bilateral adrenal enlargement with multiple hypodense macronodules which reached a maximum diameter of 67 mm and 49 mm. Considering a PBMAH diagnosis, the stimulation tests to assess aberrant receptors were performed following *Lacroix et al* protocol, but there was no evidence of positive response. The patient initiated metyrapone, controlling the hypercortisolism with 250 mg twice daily. Unilateral adrenalectomy of the largest adrenal gland was considered and uneventfully performed. Histopathologic evaluation revealed an adrenal cortex macronodular hyperplasia, compatible with the PBMAH diagnosis. After surgery, blood pressure returned to normal levels, allowing antihypertensive medication to be suspended two weeks afterwards, and 24 h urinary cortisol normalized. The patient also reported improved well-being and weight loss was documented. One month after surgery, she remained on hydrocortisone replacement, under close surveillance.
Discussion and Conclusions
In this case, secondary hypertension evaluation revealed hypercortisolism and documented adrenal macronodules favouring PBMAH diagnosis. Despite being frequent, aberrant receptors were not present, precluding targeted medical treatment. Unilateral adrenalectomy may offer clinical and biochemical benefits while avoiding hormone replacement, nevertheless, long term follow-up is required since disease recurrence has been reported with this approach.

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EP79

Preoperative management of Pheochromocytoma with fluctuation of Blood Pressure: A case report

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Introduction
Pheochromocytoma is a rare tumor of chromaffin cells localized in the adrenal gland. It is responsible of secretion of catecholamines in a supra physiologic amount, leading to hypertension. Some patients may present with hypotension despite having high circulating levels of catecholamines. The challenge is to stabilize blood pressure by medication in cases with fluctuation of blood pressure.
Case presentation
49-year-old woman suffered from recurrent right hypochondrium pain and paroxystic headache, palpitations and sweats. She has no history of hypertension and no family history of pheochromocytoma. Urinary 24-h excretion levels of epinephrine, norepinephrine, and dopamine, were highly increased. Abdominal CT Scan showed a right adrenal mass measuring 71×86 cm, discreetly enhanced after injection of PDC and with areas of cystitis and necrosis. After being hospitalized, monitoring of blood pressure and heart rate showed an extreme fluctuation with systolic pressure peaks reaching 210 mmHg and systolic pressure nadir reaching 70 mmHg; and the HR fluctuates from 65 to 120 beats/min. Doxazosin was orally administrated starting by a dose of 1 mg/day, then 2 mg/day, 10 days before surgery. However, the patient kept the fluctuations until day 6 of treatment. Intravenous fluids were introduced 3 days before surgery. Right adrenalectomy was performed through laparotomy with two incidental high BP episodes during surgery. Histological examination confirmed the Pheochromocytoma. BP and HR remain stable after adrenalectomy.
Discussion
Hypotension and BP fluctuation are rare phenomena in patients with pheochromocytoma. The mechanisms by which hypotension and BP fluctuation occur in these patients despite an increase in catecholamine level remain unclear. There is no consensus concerning management of hypotension and BP fluctuation. The Endocrine Society recommend a preoperative blockade (by α-adrenergic receptor blockers as the first choice) for all patients with hormonally functional pheochromocytoma despite the BP status. Some studies showed a beneficial effect of treatment with a combination of intravenous norepinephrine and doxazosin on BP fluctuation. Adrenalectomy should be performed after stabilization of BP.
Conclusion
We presented a case of Pheochromocytoma in a patient who had an important BP and HR fluctuations. The preoperative preparation must be delicate with a close monitoring of BP.
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EP80

Impact of glucocorticoid replacement therapy on anthropometric parameters in patients with Addison disease

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Introduction
Inappropriate glucocorticoid replacement therapy results in higher mortality rates in patients with Addison disease (AD), predominantly due to higher prevalence of cardiovascular diseases, disturbed glycometabolic state and altered anthropometric parameters. The aim of this study was to assess the impact of life-long corticosteroid exposure on anthropometric parameters in patients with AD.
Patients and Methods
This Tunisian cross-sectional study was conducted in the Endocrinology department of Hedi Chaker University hospital, Sfax, Tunisia, from March 2020 to July 2021, including 50 patients followed for AD for at least 5 years. Anthropometric parameters during clinical controls and at time of the study were recorded. Predictive factors of altered anthropometric parameters were assessed.
Results
Patients had a median age of 49.5 ± 13.9 years (18-87 years) and a disease duration with a mean of 13.9 ± 8.7 years (5-35 years). The mean hydrocortisone dose was 27.4 ± 6.7 mg/day. The mean cumulative dose was 374.636 ± 283.821 mg. The average weight was 72.5 kg (62-107 kg). Seventy percent of patients developed progressive weight gain that was more marked during the first-year follow-up with a mean of 7.4 kg. Average body mass index (BMI) was 28.1 kg/m^2 (21.2-45.8 kg/m^2). Overweight and obesity were recorded in 48% and 26% of patients, respectively. There was no significant correlation between BMI and disease duration nor glucocorticoid replacement dose. Mean waist circumference was 107 ± 11.8 cm (65-121 cm) for woman and 105.1 ± 9.6 cm (64-119 cm) for men. Android fat distribution was depicted in 60% of patients vs only 12% at time of diagnosis. Those patients received higher daily glucocorticoid dose (26.1 ± 7 mg/day vs 24.6 ± 6.1 mg/day, $P = 0.7$). As well, android fat distribution was significantly correlated with cumulative glucocorticoid dose (452.2 ± 301.7 mg/day vs 241.1 ± 264.2 mg/day, $P = 0.02$).
Conclusion
Conclusively, patients with AD taking long-term glucocorticoid therapy may experience altered anthropometric parameters. Consequently, it seems crucial to ensure regular monitoring of those patients in order to reduce cardiovascular complications.

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EP81

Successful management of adrenal Cushing's syndrome associated with androgen co-secreting adenoma during pregnancy: a case report

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Introduction
Adrenal Cushing's syndrome during pregnancy is rare, and few cases have been reported. It is infrequent to identify pregnant women with adenomas that have cortisol and androgen co-secretion. The diagnosis and treatment of excess cortisol during pregnancy is challenging when the patient does not want a pregnancy interruption.
Case Report
38-year-old woman with arterial hypertension for four years. During her working days, she remained upright constantly and presented back pain. As part of the approach to this pain, they requested a simple chest tomography without evidence of alterations in the thoracic spine or mediastinum, but with the incidental finding of a 35-mm right adrenal lesion, for which they requested a contrasted abdominal tomography with an adrenal gland protocol. Due to administrative delays, she could not have a timely evaluation of endocrinology. At the time of the initial evaluation, she attended at 14 weeks of gestation, a high-risk pregnancy due to advanced maternal age and pre-pregnancy hypertension. When evaluating this adrenal lesion, hypercortisolism was confirmed by two results with more than 2 to 3 times the reference value of free cortisol in 24-hour urine and adrenocorticotropic hormone less than 5 pg/ml, in addition, hyperandrogenism of adrenal origin with elevated values of 17 hydroxyprogesterone (1633 ng/dl VR: 10-120 ng/dl) and total testosterone (242 ng/dl VR: 0-50 ng/dl), excess aldosterone and catecholamines were ruled out. Pharmacological treatments for Cushing's syndrome are contraindicated during pregnancy, and the patient rejected the possibility of voluntarily terminating the pregnancy; she decided to undergo resection by oncological surgery. At 22 weeks of gestation, she had a 3.5 × 3.0 × 2.5 cm adrenal adenoma resected laparoscopically without complications with subsequent remission of hypercortisolism and hyperandrogenism. Oral prednisolone was started due to adrenal insufficiency due to the slowdown in the activity of the left adrenal gland. The 38-week pregnancy was terminated by cesarean section with a healthy female neonate. The evolution was good in the follow-up one month and three months after the end of the pregnancy. However, she continued with oral corticosteroid replacement requirements and is under surveillance, awaiting a possible recovery of the hypothalamic-pituitary-adrenal axis.
Conclusion
Adrenal adenomas identified during pregnancy are a challenge, drugs are a contraindication in this scenario, and surgical resection can be performed when there is a qualified interdisciplinary team.

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EP82

Black adrenal adenoma mimicking an oncocytoma–a case report

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Introduction
Black adrenal adenomas are rare and benign. They are named after their black appearance, due to lipofuscin pigment. Most frequently black adenomas are associated with ACTH-independent Cushing's syndrome. They can also cause primary hyperaldosteronism or be nonfunctioning. Unlike most other adrenal adenomas, black adenomas exhibit high Hounsfield units (> 30) on CT, and high standard uptake value on FDG-PET.
Case presentation
A 67-year-old woman was diagnosed with lung cancer (adenocarcinoma). For staging purposes, she underwent thoraco-abdominopelvic CT and FDG-PET/CT scans. The CT scan identified a 14 mm nodule of the left adrenal gland, with spontaneous density of 34 Hounsfield units, and the PET/CT scan showed high uptake on the left adrenal gland (maximum standardized uptake value 5.3), but no significant uptake on the pulmonary nodule. Due to high suspicion for metastasis, she underwent an adrenal biopsy. Histological findings were suggestive of an adrenal oncocytoma (oncocytic cells, intracytoplasmic lipofuscin pigment, nuclear anisocarysosis, binucleation, prominent nucleolus and nuclear pseudoinclusions). She underwent an upper right lobectomy and was restaged to pT1bN0R0. The adrenal nodule was initially on active surveillance, but due to increasing dimensions to 20 mm on a follow-up CT-scan, she underwent a left adrenalectomy. No hormonal study was performed prior to the biopsy or surgeries. Macroscopically, a dark, homogeneous, well delimited lesion of 1.8 × 1.8 × 1.5 cm was identified on the surgical specimen. The histological exam was compatible with an adrenal cortex black adenoma, with a conventional Weiss score of 2. Eleven days after the adrenalectomy, the patient presented to the emergency room with fatigue, abdominal pain, hypotension, and hyponatremia. She had *rubeosis faciei* and abdominal fat deposition, but no other stigmata of Cushing's syndrome. Occasional serum cortisol was 1.8 µg/dl and 1.5 µg/dl, at 5 A.M. and 7 A.M. respectively. A diagnosis of acute adrenal insufficiency was made, and the patient received intravenous hydrocortisone, which was weaned to a physiologic oral dose during one week of hospitalization. The onset of adrenal failure after unilateral adrenalectomy with an intact contralateral adrenal gland, led the medical team to presume a previously undiagnosed endogenous hypercortisolism in relation to the adrenal black adenoma. Recovery of the axis has not been assessed yet.
Conclusion
Black adenomas are benign but present with features suggestive of malignancy on both PET and CT scans. They can be associated with hypercortisolism and

hyperaldosteronism. This case highlights the importance of performing hormonal studies despite high suspicion for primary or secondary malignancy.

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EP83

Primary adrenal insufficiency in the context of small-cell neuroendocrine prostate cancer

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Introduction
The small-cell neuroendocrine prostate carcinoma (SCPC) is rare, highly aggressive and usually transforms from prostate adenocarcinoma (PAC) after androgen deprivation therapy (ADT).
Case Report
A 66-year-old man had a three-year history of high-grade PAC with high burden disease (abdominal lymph node and bone metastasis) at presentation (09/2019). On the initial staging evaluation, the CT scan documented a 20 mm left adrenal nodule compatible with adenoma. No assessment for hormone excess was performed. He initiated long-term ADT and completed six cycles of palliative chemotherapy with docetaxel. He had good clinical, biochemical (PSA decreased from 18.84 to less than 1 ng/ml) and imaging responses on conventional exams, with best response stable disease. Nineteen months after diagnosis, the left adrenal nodule grew to 29 mm and a de novo 13 mm right adrenal nodule was documented. After additional seven months, dimensional progression (on the left to 46 mm; on the right to 17 mm) and features suspicious for malignancy were observed. An MRI confirmed bilateral adrenal metastasis with further progression after six months (on the left to 50 mm; on the right to 45 mm). Analytically there was evidence of hypocortisolism, and the Endocrinology Department was consulted. Clinically he complained of moderate asthenia, anorexia, and low normal blood pressure for four months. On physical examination was noted mucocutaneous hyperpigmentation and the blood pressure was 110/70 mmHg. Further endocrine studies confirmed primary adrenal insufficiency: morning cortisol 6.7 µg/dl, ACTH 765.80 pg/ml, unmeasurable DHEA-s and aldosterone, high plasma renin activity; normal-high potassium; normal sodium and fasting glucose. Functional pheochromocytoma was excluded. He was started on hydrocortisone at supraphysiological doses, with marked clinical improvement. The 18F-FDG PET/CT revealed enlarged nodular adrenal glands with moderate tracer uptake and slight prostate heterogeneous tracer uptake, with no other abnormal foci. The adrenal mass biopsy revealed a small-cell neuroendocrine carcinoma; immunohistochemical staining was positive for CK AE1/AE3, synaptophysin, chromogranin and PSA (negative for CK7, CK20, MelanA and TTF1); Ki67 $>$ 50%. It was decided to start cisplatin and etoposide.
Discussion
We describe an exceptional rare case of bilateral adrenal metastasis causing adrenal insufficiency, from a prostate cancer that possibly transformed from PAC to SCPC after ADT. Indeed, adrenal insufficiency is uncommon in the context of bilateral adrenal metastasis and the adrenal glands are unusual sites of metastatic prostate cancer. The SCPC usually presents mixed with classic PAC and carries a poor prognosis with rapid disease progression and limited survival.

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EP84

Addison disease in type 2 auto immune polyglandular syndrome

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Introduction
Autoimmune polyglandular syndrome APS type 2 is a rare polygenic disease associationg endocrine autoimmune affection but also other auto immune diseases. The chronology is variable. We report in this context a case of APS associating a Hashimoto thyroiditis, a premature ovarian deficiency and an Addison disease revealed later.
Case Report
A 33 year-old women consulted in 2018 for asthenia and spaniomennorrhea. The diagnosis of peripheral hypothyroiditis was retained. Antibodies Ab anti thyroperoxydase were positive. It was a Hashimoto thyroiditis. The patient was treated with levothyroxine. Menstrual disturbance persisted. Gonadic assessment was performed showing low oestradiol and an elevated FSH. Premature ovarian insufficiency was retained. Iatrogenic causes were excluded in anamnesis. There were no signs for genetic causes as a dysmorphic syndrome. A auto immune origin is the most probable etiology. She was treated with oesro-progestatif hormonal therapy. Four years later, she consulted the emergency department for asthenia, abdominal pain and vomiting. Hyponatremia with kaliema at the upper range were objectified. Peripheral adrenal insufficency was confirmed by a low cortisol at 66 nmol/l (n $>$ 138 nmol/l) and an elevated ACTH at 440 pmol/l. She was treated with parenteral hydrocortisone HC relayed with oral HC 25 mg divided into 2 doses. Aldosteron level was low. A treatement with Fludrocortisone was associated. CT Scan showed atrophic adrenal glands without calcifications. The Ab anti 21 hydroxylase were positive at 6.6 U/ml (n $<$ 0.4). Type 2 APS was retained. In the screening for the other auto immune affection, there was no signs of vitiligo, no chronic diarrhea, ab anti transglutaminase were negative. No diabetes. No arthralgia or other signs of systemic affection. Normocytaire anemia was present, vitamine B12 was normal but ab anti parietal cell were positive. A gastroscopy was prescribed searching for gastric atrophia as part of Biermer disease. The patient were referred for a genetic study. Results are pending.
Comments and Conclusions
APS type 2 is a genetic disease, implicating several genes, as genes coding to class II major histo-compatibility complex, Cytotoxic T Lymphocyte Associated Antigen-4 and others. The presence of two auto immune gandular affections, must incitate clinicians to look for other auto immune affection either endocrinopathie or systemic diseases. As shows our case report, the disease may appear at any time. So that, auto immune screening should not be overlooked during follow up, especially addison disease which is a life threatining affection.

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EP85

Late-onset 21-hydroxylase deficiency: A case report

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Introduction
Partial 21-hydroxylase deficiency is a genetic autosomal recessive disorder responsible for accumulation of the precursor upstream of the enzyme block, 17-hydroxyprogesterone (17OHP), and excessive androgen production.
Observation
A 29-year-old woman consulted for hirsutism with a Ferriman–Gallwey score of 25. There were no signs of Cushing syndrome and no abnormalities of sexual development. The Laboratory results revealed testosterone level of 0.76 ng/ml with elevated Δ4 androstenedione to 4.5 ng/ml. Cortisol level was comfortable at 180 ng/ml and 17OHP was elevated to 6 ng/ml and then to 14.6 ng/ml after Synacthen test confirming 21-hydroxylase deficiency. Pelvic ultrasound and adrenal CT scanning were normal.
Discussion
Partial 21-hydroxylase deficiency is responsible for more than 95% of late-onset congenital adrenal hyperplasia. It is distinct from the early so-called "classic" form due to a complete or major block and which results in virilization of a female child and/or syndrome of salt depletion. It usually reveals itself at puberty, sometimes years later. The most frequent reason for consultation is hirsutism, and justifies a Synacthen test with 17OHP in all cases of hirsutism with biological hyperandrogenism. The diagnosis is based on a 17OHP level above 10 ng/ml after stimulation. Management should include a molecular study of the CYP21B gene and a family investigation should be proposed.

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EP86

Addisonian crisis unmasked by levothyroxine replacement in a patient admitted with suspected septic shock

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Hypothyroidism due to autoimmune aetiology can be associated with other autoimmune conditions such as Type 1 Diabetes Mellitus (T1DM) and primary adrenal insufficiency. Ruling out primary adrenal insufficiency is important in any patient with suspected autoimmune hypothyroidism.
Case
43-year-old female complaining of general lethargy, sore throat, and neck pain. She was found to be hyponatraemic (Na + 130) after being reviewed by the GP and was advised to attend Accident and Emergency. The patient was admitted with suspected septic shock and severe hyponatremia (Na 112). Her background includes PCOS, recently diagnosed hypothyroidism, and Acalculous Cholecystitis. In her first admission, she was found to be hypothyroid and was started on levothyroxine replacement. 6 weeks after starting treatment, she was admitted once more with severe lethargy, hyponatremia with low cortisol. She underwent further testing including a short synacthen test which showed a suboptimal response. Adrenal antibodies were positive. During her inpatient stay she was treated with IV hydrocortisone and then discharge home on oral hydrocortisone and fludrocortisone. She remains stable and her sodium level has normalized.
Discussion
Autoimmune polyendocrine syndrome II consists of autoimmune hypothyroidism, primary adrenal insufficiency, and/or T1DM (Smith & Gerritis 2019). Levothyroxine replacement augments liver corticosteroid metabolism, consequently precipitating an adrenal crisis in an individual with low cortisol (Betterle et al 2004). It is therefore important to keep a high index of suspicion of primary adrenal insufficiency in patients with autoimmune hypothyroidism. It is also important to ensure sufficient testing is carried out to allow for appropriate glucocorticoid replacement to be given prior to levothyroxine replacement in affected individuals.
Conclusion
Ruling out adrenal insufficiency prior to thyroxine replacement in a patient with hypothyroidism is vital given the co-existence of these autoimmune conditions.
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EP87

The VON Hippel-Lindau Disease, report of two cases and literature review

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Background
Von Hippel–Lindau (VHL) is a rare, autosomal dominant syndrome characterized by the development of highly vascularized tumors in multiple organs. VHL affects approximately 1 in 35,000 live births. Tumors associated with VHL include hemangioblastom of the retina and central nervous system, pheochromocytomas, endolymphatic sac tumors of the middle ear, and epididymal or round ligament cysts. In 80% of patients, VHL disease is familial caused by mutations in the *VHL* gene and in about 20% of cases results from de novo mutations. Penetrance is 90% by the age of 65 years, with the mean age at diagnosis being 26 years.
Case Report
We reported two cases of VHL disease reveled by different clinical presentation: pheochromocytoma and cerebellus hemangioblastoma, at different age 48 and 26 years old. Both had the complete spectrum of disease included cerebellus hemangioblastoma, retinal hemangioblastoma, pheochromocytoma, pancreas tumors and renal cell carcinoma.
Conclusion
The von Hippel-Lindau disease is a familial cancer predisposition syndrome. Regular follow-up, early detection and management of tumors reduce morbidity and mortality.

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EP88

Descriptive analysis of pheochromocytomas and paragangliomas in the southern area of Granada

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Introduction and Objectives
Pheochromocytomas and paragangliomas are rare neuroendocrine tumors derived from enterochromaffin tissue, mostly catecholamine-producing, adrenal gland (PCC) or extra-adrenal paraganglia (PGL). We were struck by the high incidence of these in our health care area, so we decided to study them. The aim of this work is to evaluate the clinical characteristics and epidemiological factors of patients diagnosed with PCC or PGL.
Material and Methods
Retrospective descriptive observational study analyzing patients diagnosed with PCC or PGL at the Hospital Universitario Clínico San Cecilio of Granada from 01/01/2018 to 31/122021. Clinical, radiological and pathological variables are measured. The analysis was performed with SPSS 15.0.
Results
18 cases were diagnosed in 4 years, which is equivalent to a mean incidence of 10.27 cases/1000000 people/year, which is higher than the figure described in the literature (2-8 cases/1000000 people/year). 15 were PCC and 3, PGL, 72.2% were women, with a mean age of 49.17 ± 15.59 years. The 61.2% were diagnosed by compatible symptoms, 27.8% were incidentalomas and 11.1% by screening in mutation carriers. The mean size measured by CT was 45.22 ± 23.02 mm. Tc-99m MIBI scintigraphy was also performed in 72.2% of cases, with positive uptake in 76.9%. Chromogranin A was elevated in 80%. Genetic test was performed in 76.5%, 5 of them had mutations. Sixteen of the 18 were operated by laparoscopy and alpha and beta blockade was performed in all of them and previous embolization in 2 of them.
Conclusions
Our suspicion about the high incidence of these tumors in our area is confirmed. We see that the diagnostic form is very varied. We found 38.46% of hereditary forms, in agreement with what has been described in the literature, 83.3% presenting some predictive factor of greater aggressiveness. We did not find any case with metastasis.

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EP89

Pheochromocytomas: presentation and diagnosis

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Introduction
Pheochromocytomas are rare, mostly benign catecholamine-producing neuroendocrine tumors. Clinical manifestations are heterogenous, including persistent or paroxysmal hypertension, sweating, palpitation and headaches known as Menard triad. Diagnostic approach is based on demonstration of catecholamine excess and tumor localization. Our study aimed to describe clinico-biological and radiological features of pheochromocytomas.
Methods
We conducted a retrospective study including 34 patients with pheochromocytoma, who were admitted into the endocrinology department of Charles Nicolle hospital from 2005 to 2022. Data were extracted from medical records.
Results
The mean age at diagnosis was 48.1 ± 14.3 years [extremes:14-72] with a sex ratio (F/M) of 2.4. Hypertension, diabetes, coronary disease and chronic kidney disease were detected in 77, 27, 6 and 20% of cases, respectively. Screening for pheochromocytoma was motivated by adrenal incidentalomas, resistant hypertension, hypertension at a young age and Menard triad in 59, 12, 18 and 12% of cases, respectively. The median (IQR) metanephrine level was 200 (112.5-1369.5) µg/day and median (IQR) normetanephrine level was 1233.5 (565-5199.3) µg/day. On computed tomography, 53% of cases had a right adrenal tumor. Only one patient had bilateral tumors. Mean tumor size was 49.4 ± 22.6 mm [extremes :10-100]. I-123 MIBG scintigraphy was performed in only nine patients with positive uptake.
Conclusion
Pheochromocytomas presentation is highly variable and can mimic other diseases. Because of cardiovascular complications, pheochromocytomas represent a potentially lethal condition, thus requiring early identification and management.

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EP90

Multifocal paraganglioma due to SDHB mutation: On purpose of one clinical case

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The mutations of succinate dehydrogenase subunits (SDHA, SDHB, SDHC, SDHD) are linked with a predisposition to develop pheochromocytoma and paraganglioma, often in diferent locations of the body. With greater acces to genetic tests, current estimations suggest that 40-50% of pheocromocytoma and paraganglioma cases are inherited and half of them are due to SDH mutations. These mutations can be associated with other tumours like renal carcinomas, gastrointestinal stroma tumours and pituitary adenomas. Affectation of subunit B is described with the most probability of malignant illness in the type 4 paraganglioma syndrome. We report a case of a patient who presented with multifocal paraganglioma and prolactinoma secondary to SDHB mutation, followed in our center in Alcorcon (Madrid) in the year 2022.
Case Report
24 year old woman with no medical background and no remarkable familiar history. Derived after finding of pituitary macroadenoma on MRI (23×14×17 mm imprinting optic chiasma) in the context of amenorrhea and elevated serum prolactine (266 ng/ml). This study also inform a incidental lesion in left yugular región inferior to craneal base, that could be a 34 mm tympanic glomus. With normal visual field testing, Cabergoline is initiated to manage hyperprolactinemia and reduce macroadenoma volume. Posterior hormone study only detected subtle elevation of noradrenaline and normetanefrine in 24 hours urianalysis. MIBI-scintigraphy was negative in the possible glomus but there was pathologic deposit in the mid abdomen which was described in a subsequent body CT as another 30 mm intrabdominal paraganglioma. Confirmed these two hypermetabolic nodules in a 18-FDG PET imaging with high expression of somatostatin receptors in a Octreoscan. We decided to first resect the abdominal nodule with previous alfa-blocking with Doxazosine, confirming histological and inmunohistochemical characteristics of sympathetic paraganglioma. The genetic study demonstrated that the patient bear the mutation c166_170CCTCA of the SDHB gene. Surgery of the yugular lesion was dismissed, opting for radiotherapy. Currect prolactine and catecholamine values are normal. Genetic screening of the patient's family still pending.
Conclusion
Mutations causing the pheochromocytoma/paranganglioma can be linked with pituitary adenomas, specially the SDH ezymatic complex. Genetic screening should be performed in all patients with these two entities alongside with a mangement in accordance with practice guidelines.

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EP91

Connshing syndrome: A case of late appeal and dilemmas in the diagnosis

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Introduction
Connshing syndrome is a rare disease characterized by mixed overproduction of mineralocorticoids and glucocorticoids from adrenal adenoma. We will describe a clinical case that illustrates a rare combination of aldosterone-cortisol co-secreting formation of the left adrenal gland against a background of bilateral macronodular adrenal hyperplasia, and the role of diagnostic methods in determining appropriate tactics for patient treatment.
Case Description
In January 2022, 49-year-old male was admitted to the Endocrinology Research Centre with complaints of increased blood pressure of 220/110 mm Hg, despite multicomponent antihypertensive therapy. According to the hormonal profile, primary hyperaldosteronism was confirmed (aldosterone 2770 pmol/l was increased, renin 0.5 mU/l, and hypokalemia was 2.71 mmol/l against a background of discontinuation of drugs that affect the renin-angiotensin system). ACTH-independent hypercortisolism was confirmed (cortisol in saliva in the evening was 60.33 nmol/l, dexamethasone suppression test was negative (cortisol was 238.8 nmol/l in the morning), ACTH in the morning was 4.88 pg/ml) . Once spironolactone (250 mg per day) was introduced in addition to moxonidine (0.6 mg per day), nifedipine (90 mg per day), doxazosin (6 mg per day), the patient's blood pressure and potassium was stabilized. As a result of MSCT of the abdominal cavity, the formation 30×35×41 mm in the left adrenal gland and the formation is 32×18×17 mm in the right adrenal gland were observed. The density was 17 HU in the native phase in the left adrenal gland, the absolute washout coefficient was 93%, the density was 9 HU in the native phase in the right adrenal gland, the absolute washout coefficient was 72%. To lateralize the side of aldosterone hyperproduction, adrenal vein sampling was performed. Unilateral hyperproduction of aldosterone on the left was confirmed (selectivity coefficient on the left was 27.5, on the right was 4.2 (both more than 3.0). The lateralizing gradient on the left was 2.8 (more than 2.0). Taking into account hypercortisolemia, a calculation was carried out on plasma normetanephrine levels. Laparoscopic left-sided adrenalectomy was performed in August of 2022. After surgical treatment, spironolactone was discontinued, but the patient was forced to take multicomponent antihypertensive therapy due to nephropathy (C3bA3) and a long history of arterial hypertension due to untimely treatment.
Conclusion
Primary hyperaldosteronism is associated with increased cardiovascular risk, and hypercortisolism increases the risk of developing diabetes mellitus and osteoporosis. This case demonstrates the consequences of a late diagnosis of the mixed overproduction of mineralocorticoids and glucocorticoids caused by adrenal adenoma.

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EP92

A case of a black adrenal adenoma with autonomous cortisol secretion

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Introduction
Adrenal incidentalomas are a frequent finding (1.4-7.3% on abdominal CT) and increasingly common with age, obesity, diabetes and hypertension. When approaching adrenal masses, clinicians should exclude malignancy and hormonal hypersecretion. Black adrenal adenomas (BAA), first reported in 1938, are rare benign adrenocortical tumours with black/brown appearance, containing lipofuscin. Most are non-functional, rarely inducing hypercortisolism. We present a case of a woman with a BAA and autonomous cortisol secretion(ACS), with great response to surgery.
Case Report
Female, 58 years-old. Referred to the Endocrinology consult in February 2019 for a left adrenal incidentaloma, diagnosed in 2017, in a colon cancer follow-up CT. She complained of insomnia but denied headaches, hypertensive crisis, spells, proximal muscular weakness, weight gain, hirsutism, previous cardiovascular events. Medical history: arterial hypertension, type 2 diabetes *mellitus*, dyslipidemia, depression, and colon carcinoma treated with right colectomy in 2017. Medication: perindopril, indapamide, amlodipine, metformin, dulaglutide, empagliflozin, insulin glargine, lorazepam, venlafaxine, mirtazapine, amissulpride, rosuvastatin and ezetimibe. No relevant family history. Physical examination: round facies and supraclavicular fat pads. Weight 68.5 kg, height 1.50 m, BMI 30.4 kg/m2. BP 120/80 mmHg, HR 95 bpm. No hirsutism, *acantosis nigricans*, abdominal striae or bruising. Initial workup showed urinary free cortisol 129.6 and 118.24 µg/24 h, cortisol after 1 mg dexamethasone 13.1 and 16.9 µg/dl, urinary free cortisol in spot urine 36.2 nmol/mmol Cr, late-night salivary cortisol 0.278 µg/dl and 0.258 µg/dl, ACTH < 5.00 pg/ml. Plasma and urinary metanephrines, aldosterone-renin ratio, TSH, creatinine and potassium were normal. HbA1c 10.9%, total cholesterol 127 mg/dl, triglycerides 333 mg/dl, LDL-c 23 mg/dl. CT: Nodule in the left adrenal gland, 25 mm, density not compatible with adenoma. MRI: Solid oval nodule in the left adrenal gland, 25 mm, absence of fat content. Osteodensitometry: lumbar spine T-score -3.4.
Diagnosis
Adrenal adenoma with ACS and multiple comorbidities (hypertension, hypertriglyceridemia, diabetes and osteoporosis).
Treatment
Left adrenalectomy in June 2021. Histology: cortical adrenal adenoma. Abundant pigment suggesting a black adenoma. Follow-up: She lost 13 kg and suspended insulin and most hypertensive agents. Transient hypocortisolism, treated with hidrocortisone. HbA1c 6.3%, morning cortisol 3.4 µg/dl, ACTH 39.5 pg/ml, total-cholesterol 122 mg/dl, triglycerides 363 mg/dl, LDL-c 38 mg/dl.
Discussion
This case highlights the importance of treating hypercortisolism to effectively control its comorbidities, cardiovascular risk factors and quality of life. In our patient, ACS originated from a BAA. Functional BAAs usually exceed 20 mm in diameter, which was the case of our patient. After surgery, there was marked

improvement of hypercortisolism-associated conditions. Therefore, early detection of Cushing syndrome in adrenal incidentalomas is essential, especially when multiple comorbidities are present and undercontrolled with medication.

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Adrenal Venous Sampling in a patient with bilateral adrenal adenomas and Cushing's syndrome

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Introduction
Adrenal Cushing's syndrome accounts for 15-20% of all the causes of endogenous hypercortisolism, mainly due to unilateral adenomas and adrenal cancer. Approximately 9-17% of patients with ACTH-independent Cushing's syndrome have bilateral adrenal adenomas. Subsequently, their management is quite demanding. The main difficulty lies in distinguishing between a functional and a non-functional adrenal mass, since this cannot be reliably achieved by routine imaging and laboratory tests. Although adrenal-venous-sampling(AVS) is a widely used method for the diagnosis of primary hyperaldosteronism, it's utility in distinguishing bilateral or unilateral cortisol overproduction, has only been evaluated by a few studies.
Case Report
A 68-year-old man, was referred to our department due to severe osteoporosis and vertebral fractures. The patient had a history of 4.5 cm right adrenal adenoma known for the past 15 years. At that time, according to the clinical evaluation and laboratory findings, no adrenal dysfunction was detected and the possibility of malignancy was ruled out. For this reason, despite medical recommendations, he did not wish to be operated on. However, 3 years ago, a slight increase in the size of the adenoma (5.5× 5.4 cm) and a marginally increased urinary-free-cortisol (UFC) 160 μg/24 h (20-90) were found. During the next months he reported low back pain, steadily worsening proximal muscle wasting and weakness, while the diagnosis of severe osteoporosis and vertebral fractures was made. Upon his arrival at our department, he had typical signs of hypercortisolism. New imaging and laboratory tests were performed. The Computed-Tomography (CT) showed the known adenoma, as well as the presence of a 1 cm adenoma in the left adrenal gland. Both, baseline and overnight 1 mg Dexamethasone-suppression-test (DST), cortisol and ACTH values, established the diagnosis of Cushing's syndrome. The patient underwent adrenal-venous-sampling (AVS), to determine the location of cortisol hypersecretion, because bilateral adrenalectomy was extremely likely. Adrenaline was used as reference hormone for Selectivity-Index(SI) and Lateralization- index (LI), and the results were compatible with hypersecretion of the right adenoma, therefore a right adrenalectomy was performed. The patient's postoperative course was satisfactory, with a gradual improvement of all the affected metabolic factors(especially bone metabolism). He continues to need hormone replacement with hydrocortisone one year after surgery.
Conclusion
Adrenal venous sampling (AVS), in patients with Cushing's syndrome and bilateral adrenal adenomas, is a useful tool, for distinguishing between bilateral and unilateral cortisol hypersecretion. However, the results require careful evaluation, along with clinical, biochemical and imaging findings. Larger studies are needed, to establish a specific method of performing and interpreting this test.

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EP94

Case report: Management of Mild Autonomous Cortisol Secretion

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Introduction
Mild autonomous cortisol secretion (MACS) is a term used to describe biochemical evidence of abnormal cortisol secretion in patients with adrenocortical adenomas (ACA), but without the classical external manifestations of overt Cushing's syndrome (CS).
Materials and Methods
In this study, we report a case of patient who presents mild autonomous cortisol secretion among incidentally discovered adrenal masses; followed in unit of the endocrinology, diabetology, metabolic diseases and nutrition department of the Mohammed VI University Hospital of Marrakesh.
Case Report
A 68-year-old woman with a history of well-controlled hypertension and diabete presents to our department for etiological assessment of an adrenal incidentaloma.. adrenal scan confirms a diagnosis of an incidental right adrenal nodule measuring 27× 26 mm is also identified having an density of 33UH and washout >50%, the patient's physical examination is unremarkable and she does not have any overt Cushingoid features or midline back pain or paroxysmal attacks. Biochemical investigations revealed a morning cortisol following 1 mg of dexamethasone is 2 μg/dl .A normal serum potassium and methoxylated derivatives in urine are normal. A diagnosis of a mild autonomous cortisol secretion was made and given the relatively mild degree of cortisol excess and well-controlled Comorbidities a conservative management is chosen, she should undergo annual clinical reassessments. If she develops new or worsening cortisol-related comorbidities, she should undergo further biochemical testing and reconsideration of adrenalectomy.
Discussion
Mild autonomous cortisol secretion is a term used to describe biochemical evidence of abnormal cortisol secretion in patients with ACA, but without the classical external manifestations of overt CS, such as central muscle weakness, adipose tissue redistribution, and skin fragility. Various terms have been used to describe MACS, such as "subclinical Cushing's syndrome" and "subclinical hypercortisolism"; however, the term "subclinical" is inaccurate, as these patients present with higher prevalence of adverse cardiovascular risk factors, such as diabetes mellitus type 2 (DM2), hypertension, dyslipidemia, obesity, increased rates ofcardiovascular disease, metabolic bone disease, and highermortality rates, when compared with patients with nonfunctioning adrenal tumors (NFAT). The management of patients with an incidentally discovered adrenal adenoma who do not have overt Cushing's syndrome but who have MACS is more controversial as the available studies comparing outcomes of adrenalectomy vs conservative management have been generally small, observational in nature, and heterogeneous.
Conclusion
Future studies with adequate randomization and follow-up to assess adverse clinical endpoints are needed to determine the optimal management and follow-up of patients with MACS.

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EP95

Primary hyperaldosteronism and renal failure: Diagnostic challenges, a case study

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Introduction
The diagnosis of primary hyperaldosteronism (PAH) is based on the realization of the renin aldosterone ratio (RAR). The presence of renal insufficiency (RI) in a hypertensive patient complicates this diagnosis by affecting various biological assays.
Observation
We report the case of 25-year-old female, with a personal history of primary hypothyroidism, hypertension diagnosed at age 21 and severe renal insufficiency developed during a pregnancy carried to term at the age of 22. Creatinine clearance was 24 ml/min with a tendency to hypokalaemia. Computed tomography of the adrenal glands revealed a 17 mm left adrenal adenoma. The biological assessment showed an excess of aldosterone (2481 pmol/l) with an unsuppressed renin activity (16.02 mIU/l). The RAR came back positive at 154.69 ($n<64$). The diagnosis of Conn's syndrome was retained. The patient underwent left adrenalectomy with improvement in blood pressure and renal function.
Discussion
The interpretation of the RAR in the context of renal failure is difficult with few data in the literature. It has been previously reported that the RAR is higher in renal failure with a risk of false positives. Recent work has shown that renal insufficiency is on the contrary responsible for a reduction in the RAR by an

increase in renin with a risk of false negative results. In renal impairment, lower RAR thresholds should be considered.

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EP96

Retrospective Evaluation and Characteristics of Bilateral Adrenal Masses Followed Up in the Endocrinology Clinic of Ondokuz Mayıs University Hospital Between 2008 and 2022

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Background
Adrenal incidentalomas are defined as clinically silent adrenal masses >1 cm in size and are detected in up to 10% of patients during imaging procedures performed for unrelated conditions. 17% and 23% of incidentally detected adrenal lesions were reported to be bilateral. The bilateral adrenal tumors include metastasis, lymphoma, neuroblastoma, pheochromocytoma, adenoma and myelolipoma. Non-neoplastic bilateral adrenal masses include infectious processes and hematomas.
Methods and Design
A retrospective review of all patients with bilateral adrenal masses who are detected in Ondokuz Mayıs University Endocrinology Clinic from 2008 to 2022 was performed. Gender, patient and diagnosis age, diameter and HU of each masses, follow- up time, imaging type, basal cortisole, ACTH, DHEAS and 17-OH Progesterone level, 1-mg dexametahasone supression test (DST) and 2-day-2 mg DST, DHEAS, 17-OH Progesteron, plasma Aldosteron(PA), plazma Renin activity(PRA), PA/PRA ratio, Saline Infusion Test, adrenal venous sampling, 24-hour-urine catecholamines and if operated, type and localization is reported.
Results
In this study, 222 patients was involved. The median age of all patients was 62.22 (range 51-72 years) and median diagnosis age was 57.58 (47-67 years). 50.2% ($n=127$) was women and 42.8% ($n=95$) was men. 120 patients (54.1%) had non-functional adenomas while 10 (4.5%) had cushing, 4 (1.8%) had pheochromocytoma, 8 patients (3.6%) had primary hyperaldosteronism, 1 (0.5%) had myelolipoma, 7 (3.2%) had other metastatic malignancies, 17 had mild autonomous cortisol secretion (MACS) and 55 (24.8%) was not properly followed. 191 patients (89.3%) didn't have any operation, while 10 (4.7%) underwent right, 9 (4.2%) left and 4 (1.9%) bilateral adrenalectomy. The operation types were 18 (78.3%) laparoscopic and 5 (21.7%) open. 23 patients that underwent adrenalectomy had a follow up of median 16 (0-187) months, while the remaining 191 (0-122) patients had a follow-up of median 5 months (P: 0.031). Diameter of right adrenal was 40 mm for the operated ($P<0.001$). Left adrenal diameter was 22 mm for the operated group(P: 0.032). 208 patients who had 24-hour-urine catecholamines sample, 4 (17.4%) were elevated in the operated group and 3 (1.6%) were elevated in the non-operated (P: 0.003). The diagnosis for the masses were also statistically significant in the operated group ($P<0.001$).
Conclusion
Most of the bilateral masses were non-functional. Cortisol and aldosterone secretion are the main causes of functional adenomas. No cases of primary adrenal malignancy were diagnosed besides that metastatic malignancies. Mass diameter for both sides and follow up time were increased in the operation group.

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EP97

Exogenous hypercortisolism after long-term transcutaneous use of clobetasol propionate in the treatment of psoriasis (a clinical case)

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The use of topical corticosteroids in the treatment of dermatosis, which includes psoriasis, is a common approach. With local use of corticosteroids, an increase in the concentration of corticosteroids in the area of the inflammatory process is noted, therefore local corticosteroids are believed not to have a suppressive effect on the function of the adrenal glands.
Purpose
To demonstrate a side effect of hypercortisolism after uncontrolled long-term use of clobetasol propionate in the treatment of psoriasis.
Materials and Methods
The patient's salivary cortisol levels, as well as repeated study of cortisol and ACTH in blood plasma were determined. The patient underwent a biochemical blood test and glucose level was determined. MRI of the pituitary gland with contrast and CT scan of the adrenal glands were performed.
Results and Discussion
A 42-year-old female patient, who has been suffering from a common form of psoriasis for more than 10 years, complained of weight gain of 15 kg over the past year and stretch marks on the skin. For the last 1.5 years, she has been using clobetasol propionate 0.5 mg/g (25 g) and applied to the skin daily (without doctor's recommendations). Approximate equivalent doses of the drug in terms of prednisolone amounted from 36 mg to 72 mg per day. On examination matronism, "Cushingoid" body features, wide purple striae on the skin, psoriatic plaques on the entire surface of the body and skin of the forearms were revealed. Biochemical examination revealed hypoproteinemia and hypoalbuminemia and hyperglycemia. A hormonal study showed a suppressed level of plasma cortisol of 18.6 and 5.78 (normal value is 166-507 nmol/l), salivary cortisol (once) at 23:00 - 0.11 (normal value is 0.2-4.0 pg/ml) while maintaining a normal level of ACTH - 23.0 and 21.1 (normal value is 7.2-63.3 pg/l). Contrast-enhanced MRI of the pituitary gland (data on the adenoid pituitary gland were not obtained) and CT scan of the adrenal region (no structural sampling was identified) were performed. After the abolition of clobetasol propionate clinical signs of adrenal insufficiency were noted (hyperkalemia - 5.9 mmol/l., hypoglycemia - 2.9 mmol/l, a decrease in blood pressure to 85/70 mm Hg., the level of cortisol - 0.01 nmol/l). Thus, exogenous hypercortisolism was diagnosed. Secondary adrenal insufficiency due to long-term use of glucocorticoids was revealed. Replacement therapy with prednisolone 7.5 mg/day was prescribed; during the follow-up period (1 year), the daily dose of prednisolone decreased to 5 mg per day.
Conclusion
Clobetasol propionate has a marked inhibitory effect on the hypothalamic-pituitary-adrenal axis.

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EP98

Adrenal insufficiency secondary to steroid withdrawal: A Case Report

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Introduction
Glucocorticoids are widely used for their anti-inflammatory and immunosuppressive properties. Prolonged administration of synthetic glucocorticoids is one of the most common cause of ACTH deficiency and consequent adrenal insufficiency. Exogenous glucocorticoids interfere with and suppress HPA axis and abrupt steroid withdrawal leaves body susceptible to adrenal insufficiency. Symptoms can range from adrenal crisis to nonspecific complains of fatigue, nausea and unexplained fever. Moreover, clinical picture of adrenal insufficiency can be obscured by patient's concomitant conditions. Timely diagnosis and treatment is essential for patients with adrenal insufficiency.
Case Report
We present a case of 45 year old female, who presented to the ER with nausea, vomiting, increasing fatigue and dysuria. On further examination, patient was found to be hypotensive and had fever. Patient's medical history was significant for motor vehicle trauma that left her paraplegic and type 2 diabetes mellitus controlled with metfromin. Diagnosis of complicated UTI was made by clinical and laboratory findings and appropriate antibiotic therapy was started. Patients

condition slightly improved but she remained hypotensive and febrile. Endocrine consultation for diabetes mellitus, revealed that patient started taking dexamethasone for Covid-19 infection that improved her energy and continued to take it irregularly for 6 months without proper medical supervision. Two weeks before presentation to the ER, patient abruptly stopped taking dexamethasone. Diagnosis of adrenal insufficiency secondary to steroid withdrawal was suspected, IV hydrocortisone was started empirically with close monitoring. Patient's condition began to improve, she became afebrile and more active, her blood pressure and electrolytes stabilized. After a week, patient was discharged home with detailed plan of steroid tapering and frequent follow-ups.

Conclusion

Steroid withdrawal and adrenal insufficiency is rare and under diagnosed condition. Diagnosis of this condition remains a challenge for clinicians, as, patients may present to the ER with vague, nonspecific symptoms. While hypotension, gastrointestinal symptoms and electrolyte abnormalities are common presenting manifestations, fever as an additional possible sign of adrenal insufficiency should be kept in mind. Considering that clinical picture of adrenal insufficiency can vary greatly, it is important to take detailed medical history and to keep a high level of suspicion. Adrenal insufficiency can be life-threatening; therefore, it is crucial to diagnose and treat this disorder in time. When adrenal crisis is suspected, treatment should not be postponed for detailed diagnostic workup. Proper patient education and close monitoring of steroid tapering cannot be understated.

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EP99

Cardiovascular repercussions of glucocorticoid replacement therapy in patients with Addison disease

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Introduction

Glucocorticoid replacement therapy may result in long-term morbidities, including cardiovascular diseases which can increase cardiovascular risk. The study was aimed to assess the impact of life-long glucocorticoid replacement therapy on cardiovascular parameters in patients with Addison disease (AD).

Patients and Methods

This cross-sectional study was conducted assess cardiovascular events in patients followed for AD for at least 5 years, in the Endocrinology department of Hedi Chaker University hospital, Sfax,Tunisia, from March 2020 to July 2021.

Results

The mean age of patients was 49.5±13.9 years (18-78 years) with glucocorticoid replacement duration of 13.9 ±8.7 years (5-35 years). High blood pressure (52%) and diabetes mellitus (52%) were the most prevalent family histories. No patient had hypertension or carbohydrate metabolism disorder at the time of AD diagnosis. Average body mass index (BMI) was 28.1 kg/m^2 (21.2-45.8 kg/m^2). Overweight and obesity were recorded in 48% and 26% of patients, respectively. Carbohydrate metabolism disorder was depicted in 38% of patients after a mean glucocorticoid replacement duration of 17.5±5.4 years. Among those patients, 31.6% developed type 2 diabetes. Patients with diabetes type 2 diabetes had longer duration of glucocorticoid use (19.8 ±9.9 years vs 13.2 ±8.4 years, P=0.1) and higher daily and cumulative glucocorticoid dose (27.5±5 mg/day vs 25.6 ±6.9 mg/day, P=0.4; 506, 2±277, 2 mg vs 355, 4±282, 9 mg P=0.1) than those with normoglycemia, but without significant correlation. Sixteen percent of patients developed hyperlipidemia after a mean glucocorticoid replacement duration of 13.6 years (mixed dyslipidemia in 5 patients, isolated hypercholesterolemia in one patient, hypertriglyceridemia in 2 patients and low HDL-cholesterol level in 5 patients). As well, patients having disturbed lipid balance had higher daily glucocorticoid dose but without significant difference (26.5±7.1 mg/day vs 25.6±6.7 mg/day,P=0.7). Hypertension occurred in 14% of patients after a mean glucocorticoid use duration of 9.5 years (2-21 years) and two patients developed coronary artery disease. There was no significant correlation between hypertension and cumulative hydrocortisone dose nor duration of glucocorticoid replacement therapy. Metabolic syndrome was noted in 24% of patients and its occurrence was significantly correlated with daily hydrocortisone dose (26.9 ±6.6 mg/day vs 22.3 ±5.9 mg/day, P=0.04).

Conclusion

Our results underline the importance of close monitoring of cardiovascular risk factors in patients with AD in order to reduce cardiovascular repercussions of long-term glucocorticoid replacement therapy.

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EP100

Delayed partial primary hypoadrenalism following therapeutic and imaging radiation exposure of the adrenal glands

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A 73 year old female presented with a 5-year history of fatigue, anorexia and weight loss of 15 kg. Her primary care physician recorded a 09:00 h cortisol of 163 nmol/l. Previous medical history was one of abdominal diffuse B-cell lymphoma 9 years earlier treated with 6 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin and prednisolone) followed by CT-guided radiotherapy. Medications were transcutaneous buprenorphine 20 mg/hour, aspirin 75 mg od and omeprazole 20 mg od. Examination confirmed a weight of 40.8 kg (55 kg 5 years earlier), signs of weight loss and supine blood pressure 180/90 mmHg with no postural drop. Pigmentation was absent. The initial impression was one of opiate-induced hypoadrenalism. Investigations at 09:00 h confirmed cortisol 268 nmol/l, ACTH 149.6 ng/l, fT4 11.0 pmol/l, fT3 5.2 pmol/l, TSH 1.75 mU/l, FSH 88.6 IU/l, LH 21.5 IU/l, prolactin 251 mU/l, IGF-1 9.5 nmol/l, sodium 136 mmol/l, potassium 4.1 mmol/l, creatinine 39 mmol/l and eGFR >90 ml/min suggesting a diagnosis of primary hypoadrenalism but adrenal antibodies were negative. Further investigations at 09:00 h confirmed cortisol 244 mmol/l, ACTH 273.3 ng/l, DHEAS <0.3 umol/l, androstenedione <0.4 nmol/l, testosterone <0.4 nmol/l, plasma renin activity 0.2 nmol/l/hour, aldosterone 337 pmol/l, followed by a Short Synacthen test with cortisol levels 404 nmol/l and 419 nmol/l at 30 and 60 minutes respectively. Review of previous imaging identified 12 CT scans (3 pre-treatment and 9 post-treatment) which confirmed a decreased adrenal size latterly. Treatment with replacement dose of hydrocortisone resulted in resolution of symptoms and weight gain of 7.4 kg over 2 months. Repeat plasma renin activity and aldosterone respectively on treatment were 0.7 nmol/l/hour and 99 pmol/l supine and 0.7 nmol/l/hour and 144 pmol/l standing. We interpret the results as indicating decreased cortisol synthesis (in the zona fasciculata) and DHEAS, androstenedione and testosterone (in the zona reticularis) with preservation of aldosterone synthesis (in the zona glomerulosa) of the adrenals. The zona fasciculata and reticularis cells comprise 75% and 10% of the volume of the adrenal cortex and their loss would explain the decreased adrenal size and impaired steroid synthesis pattern. Acute effects of therapeutic radiation on the appearance and function of the adrenal glands have been reported but not so chronic. We postulate that the combination of therapeutic radiation with superimposed imaging radiation caused the loss of adrenal cell mass and the steroid synthesis abnormities recorded and possible mechanisms of such.

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EP101

Aggravation of depressive symptoms after biochemical cure of Cushing syndrome

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Introduction
Endogenous Cushing syndrome (CS), is associated with significant morbidity (metabolic, cardiovascular, bone, psychiatric complications among others). Most complications tend to improve if hypercortisolism is controlled but some are only partially reversible or even experience temporary exacerbation.
Patients and Methods
We report 2 cases of adrenal Cushing Syndrome (CS). The first is a 72 years-old female with CS caused by bilateral macronodular adrenal hyperplasia (complicated by diabetes mellitus, arterial hypertension and osteoporosis), treated by bilateral adrenalectomy. The second patient was a 45 years- old female with CS caused by left adrenal adenoma complicated by arterial hypertension and diabetes mellitus, treated by left adrenalectomy.
Results
In the first case the postoperative evolution was complicated by severe gastrointestinal candidiasis (discovered after repetitive episodes of adrenal insufficiency despite adequate replacement with gluco- and mineralcocorticoids) and severe depressive symptoms. These necessitated starting antidepressive medication (tianeptine) with slow control of symptoms over 18 months. In the second case postoperatively the only significant symptom occurring during adequate replacement during the initial months was very severe invalidating depression, slowly improving over several months under treatment with mirtazapine and fluoxetine.
Conclusions
Shortly after successful control of hypercortisolism in certain patients exacerbation or occurrence of serious psychological/psychiatric problems is possible so all patients should be evaluated and followed closely by the endocrinologist which should promptly liaise to psychiatric team whenever needed.

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EP102

The coexistence of primary adrenal insufficiency and systemic diseases: About two cases

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Introduction
The majority of systemic diseases result from an autoimmune process. Primary adrenal insufficiency (Addisson's disease AD) is also frequently caused by an autoimmune process. Their association is rare but can be seen in the framework of autoimmune polyendocrinopathies. We report 2 observations associating an autoimmune adrenal insufficiency with a systemic disease.
Observation 1
We describe the case of a 50-year-old patient initially admitted to the intensive care unit for vomiting, diarrhea and acute dehydration. Physical examination showed melanoderma and hypotension at 80/60 mm hg.A baseline blood sample revealed hyponatremia (127 mmol/l) and hyperkalemia (5.6 mmol/l). Thus,Acute adrenal insufficiency was suspected. The patient immediately received intravenous hydrocortisone hemisuccinate with hyperhydration. The diagnosis of AD was confirmed by a low plasma cortisol level (50 nmol/l) in the face of high adrenocorticotropin hormone (ACTH) level = 1250 pg/ml). Concerning the etiological investigation, the detection of BK in the sputum analysis was negative, the chest X-ray was normal and the adrenal glands were eutrophic in the Computed tomography. However, the anti 21 hydroxylase antibodies were positive. In the framework of the search for other autoimmune diseases, we found a thyroid autoimmunity with positive ATPO of 412 UI/ml. Antinuclear antibodies, anti SSA, anti SSB and anti R052 were also positive. The patient was referred to the department of internal medicine for management of a Goujerot Sjogren syndrome in the context of very likely systemic lupus erythematosus.
Observation 2
We report the case of a 27-years-old patient who was diagnosed three years ago with Behçet's disease (BD) on the basis of the symptoms of BD triad, which included recurrent oral and genital aphthous, arthralgia and iritis. Recently, he consulted in our endocrinology department for recurrent hypoglycemia. The baseline cortisol level was low(152 nmol/l) and the adrenal insufficiency was confirmed by a stimulation test. ACTH level was high which indicated Addison's disease.
Discussion
Gougerot-Sjogren's syndrome is a systemic disease associated with a humoral immune response. The coexistence with AD has been reported in the literature. Several mechanisms could explain this association such as thrombosis of adrenal vessels,hemorrhage due to anti-phospholipid syndrome,vasculitis or direct organ involvement by an autoimmune process BD pathophysiology is controversial with conflicting data.It is believed that BD disturbs the regulation of immune system. Furthermore, few studies correlate BD with AD and found partially dysfunctional adrenal glands in BD patients.

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EP103

Steroid hormone withdrawal and autoimmunity induction

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Introduction
Pregnancy is characterized by increased secretion of estrogens and cortisol. Estrogen is used to prepare the maternal environment for the fetus. Cortisol induces a state of immunosuppression to avoid loss of the fetus, which, by definition, is at least partly a foreign organism. Parturition is characterized by estrogen and cortisol withdrawal. It leads to a rebound in immunity and may be accompanied by the development of autoimmune disease. Autoimmune thyroid disease is observed postpartum and may be related to this rebound in immunity. Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease.
Aim
The aim was to present the cases of two female patients who developed RA postpartum after the birth of their second child.
Methods
The cases of two female patients aged 40 and 42 years, respectively, who developed RA postpartum after the birth of their second child are described.
Results
The patients went into menopause immediately following the birth of their second child. RA was RF(+) anti-CCP antibody (+) and led into hospitalization of the patients for a month following parturition. Corticosteroids were administered followed by methotrexate. In long-term follow up both patients required the addition of a biologic agent and are now in remission on treatment with methotrexate and a biologic agent at the age of 79 and 81 years, respectively.
Conclusions
Oestrogen and cortisol withdrawal may have led to the development of RA immediately postpartum in the cases described herein. The development of RA postpartum has been previously reported. Amongst a large cohort of RA patients 2 were reported to develop RA postpartum. RA flare has also been reported postpartum. Additionally, autoimmune thyroid disease is known to occur postpartum, an incidence, which may also be related to steroid hormone withdrawal. In conclusion, estrogen and cortisol withdrawal may reverse the immunologically beneficial maternal profile and may lead to the development of postpartum clinical autoimmune disease.

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EP104

When pheochromocytoma occurs in the elderly: A case report

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Introduction
Pheochromocytoma is a rare neuroendocrine tumor. It is usually diagnosed in subjects between 40 and 50 years of age. The occurrence of pheochromocytoma in the elderly is much rarer and has its own particularities. We report the case of a 70-year-old female patient with invasive pheochromocytoma.
Case presentation
A 70-year-old female patient with a history type 2 diabetes for 18 years on oral antidiabetics and insulin. The history of his disease goes back to a few months with an

important weight loss, and the installation of a menard triad made of headaches, sweats and palpitations. Exploration showed a suspicious adrenal mass on abdominal CT. Urinary methoxylate assays showed very high levels of metanephrines and normetanephrines. The patient underwent a laparoscopic right adrenalectomy. Pathological examination was in favor of an invasive pheochromocytoma. During the follow-up, the methoxylated derivatives assay was negative.
Discussion
Pheochromocytoma is a benign tumor that develops at the expense of chromaffin cells and secretes catecholamines. Clinical signs are dominated by permanent or paroxysmal hypertension. It rarely occurs in elderly subjects and symptoms may be more subtle and less specific in this age group. In our patient, pheochromocytoma was revealed by weight loss and Menard's triad. It is also more common in the elderly to develop multiple or malignant pheochromocytomas. In our patient the anatomo-pathological examination showed an invasive pheochromocytoma. A meticulous clinical examination and a regular medical follow-up are essential for the detection of pheochromocytoma in the elderly subject.

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EP105

Clinical and biological features of late-onset congenital adrenal hyperplasia

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Introduction
21-hydroxylase deficiency represents 95% of congenital adrenal hyperplasia. The non-classical form manifests in women mainly by hirsutism, menstrual disorders, or infertility. We present three patients' cases.Observations: Patient N.C., 17 years old, who presented with hirsutism beginning at the age of 8 years and progressively worsening after puberty. The patient had her menarche at the age of 9 years, with short and irregular menses. Her BMI was at 27 kg/m^2. Her height was at 166 cm (+1DS), her BP was at 11/8 cm Hg. She had severe hirsutism with a Ferriman-Gallwey score of 35, and she had signs of virilization such as clitoral hypertrophy (Prader 1). Biochemical hyperandrogenism was found with a total testosterone =1.1 ng/ml, S-DHEA=5370 ng/ml, and 4-androstenedione=7 ng/ml. ACTH was high at around 95 pg/ml. Baseline cortisol level was at 220 ng/ml. Baseline 17OH progesterone was 13.6 ng/ml. An abdominal CT scan did not show adrenal hyperplasia. Patient A.F., 18 years old, presented with peripubertal hirsutism. She has a sister with a classic form of congenital adrenal hyperplasia. Her menarche occurred at the age of 12, with irregular menses leading up to a 2-year secondary amenorrhea. On examination, BP was 12/8 cm Hg. Her height was at 152 cm (-1DS), and BMI was at 31 kg/m^2. She had severe hirsutism with a Ferriman-Gallwey score of 31. She did not show signs of virilization. Total testosterone =0.4 ng/ml, S-DHEA =2650 ng/ml, and 4-androstenedione was high at 6.1 ng/ml. ACTH was at 20 pg/ml. 17O-Progesterone response to standard dose synacthen stimulation test was as follows: T0: 11 ng/ml, T30: 42 ng/ml, and T60: 42 ng/ml. Microcystic ovaries were present on pelvic ultrasound. Patient S.B., 22 years old, who presented with post-pubertal-onset hirsutism and dysmenorrhea She had a family history of diabetes. Her menarche occurred when she was 14 years old. On examination, her BP=11/7, BMI:28 kg/m2, height: 155 cm, Ferriman-Gallwey score: 26, no signs of virilization. Total testosterone: 1.1 ng/ml Baseline 17OH-progesterone level: 34 ng/ml.
Discussion
In the late-onset form of congenital adrenal hyperplasia, the clinical presentation is that of peri- or postpubertal hyperandrogenism. Hirsutism is the most common manifestation. It may be associated with signs of virilization or short stature due to premature closure of the epiphyseal plate. Menstrual disorder and anovulation are related to the permanent production of estrogens due to the aromatization of hypersecreted adrenal androgens. PCOS may be present in some cases.

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EP106

Comparison of The Clinical Course, Mortality and Morbidity Rate of the Covid 19 Disease in Patients with Cushing'' s Syndrome and Patients with Non-functional Incidentaloma

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Objective
Subclinical Cushing's Syndrome is defined as the condition of detecting moderate autonomic cortisol secretion, and it has many conditions such as diabetes, obesity, hypertension, osteoporosis, cardiovascular events, thromboembolic disease, dyslipidemia and immunosuppression comorbidities and with mortality having a relationship shown. Declared a global pandemic COVID-19 infection rapidly spreading with symptoms characterize andmortal one who can watch is a disease. COVID-19 in patients, especially respiratory have a failure in patients steroid in treatment is used in a certain phase when used steroid this treatment in the patient group important to prognosis extent of benefit provides many in the study shown. Subclinical Cushing Syndrome diagnosed patients infected with COVID 19 when, present endogenous cortisol of the height contribution to prognosis completely unknown. Endogenous cortisol height, during treatment applied with cortisol similar effect being or hypercortisolemia caused by immunosuppression status clinical disease your course to worsen are likely to contribute. This The aim of the study endogenous hypercortisolemia condition COVID-19 in patients prognosis whether your contribution that you are not is research.
Materials and Methods
Dokuz Eylul University, Faculty of Medicine, Department of Internal Medicine, Endocrinology in the Department of Science adrenal incidentaloma and Subclinical Cushing Syndrome follow-up and treated, 18 over age, (n=415) of patients biochemical examinations and viewing methods back records facing down examined, the same in time 01.01.2020- 01.10.2222 between COVID-19 testing to the results has been reached. This patientin groups COVID-19 course of illness and mortality rate was compared. Incidentaloma detected patients Subclinical Cushing Syndrome and non-functional adrenal incidentaloma in the form of patients divided into two groups. Sublinic Cushing Syndrome and non-functional incidentaloma diagnosed 1 mg of patients DST result cut off value is accepted as 1.8 µg/dl was done. Both among the group nominal variables that with square test compared.All analyzes SPSS (24.0) with the program done.
Results
In this study, we have done due to adenomas autonomous cortisol secretion there was no significant difference in the frequency of transmission of COVID-19 in patients who were diagnosed with the disease compared to the patients who did not produce hormones. At the same time, a 1 mg DST result of >1.8 µg/dl was not found to be associated with a complicated course in patients with COVID-19 positivity. However, in our study, it was found that the risk of developing complications in the course. of the COVID-19 disease increased 2.17 times in patients with SCS compared to patients with NFA.

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EP107

Acute adrenal insufficiency revealed by a convulsive crisis

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Introduction
Adrenal insufficiency is defined as a deficit in the functioning of the adrenal cortex. The acute form represents a diagnostic and therapeutic emergency, but the clinical presentation is sometimes misleading.
Observation
We report the case of a 57-year-old patient with a personal history of vitiligo, who was suffering for two months from asthenia with abdominal pain and vomiting, then he presented with a generalized tonic-clonic convulsive seizure requiring his urgent transport to the neurology department. His blood pressure was at 100/70 mmHg and the Glasgow score at 14/15. Biology showed severe hyponatremia at 119 mmol/l with hyperkaliemia at 6 mmol/l. Hormone assay confirmed the diagnosis of acute adrenal insufficiency in the presence of cortisolemia <5 µg/dl with a high ACTH level at 102.6 ng/l. The patient was immediately put on hydrocortisone sodium succinate with a marked improvement. Complementary adrenal CT showed bilateral adrenal atrophy in favor of the autoimmune origin of the adrenal insufficiency.
Discussion
Acute adrenal insufficiency is a rare pathology but which involves the vital prognosis in the short term. It must always be suspected, particularly in the face of evocative ionic disorders or a clinical manifestation not explained by another pathology. It is mainly a therapeutic emergency, even without a positive diagnostic certainty.

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EP108

Adrenocortical Carcinoma presenting as florid Cushing's Syndrome

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Introduction
Adrenocortical Carcinoma (ACC) is a rare endocrine neoplasm with poor prognosis, and an estimated incidence of approximately 2.5/1,000,000 patients. The functional state of these tumors varies from non-secretory (20%) to non-secretory. The latter category is subdivided into glucocorticoid-producing (45%) or glucocorticoid-androgen producing (45%) or androgen-producing only (10%). We report a case of a 35-year-old lady who initially presented with symptoms of Cushing's Syndrome and underwent adrenalectomy, with post-operative histology compatible with adrenocortical Carcinoma.
Case presentation
Health problems started 5 years ago, when she was diagnosed with Type 2 Diabetes Mellitus, on treatment with oral agents, at that time she underwent sleeve gastrectomy resulting to improved glycemic control and weight loss for the next 4 years. After this time, she started gaining weight again and her glycemic control deteriorated. A few weeks later, she was admitted to the hospital with complaints of diarrhea. Imaging with a Computed tomography of the abdomen and pelvis showed an incidental 30 mm left medial limb adrenal nodule with central focus of calcification with absolute washout of 76% is consistent with adrenal adenoma. A smaller 10 mm left adrenal nodule is also compatible with a lipid rich adrenal adenoma. Biochemical assessment showed failure to suppress adrenal function (overnight dexamethasone suppression test: pre-test cortisol 9 am 695 nmol/l, post-test cortisol 9 am 587 nmol/l; paired ACTH was suppressed to $<$1.5 ng/l pre-test; low-dose dexamethasone suppression test, post-test 227 nmol/l). The remaining biochemical screen showed raised 24-hour urinary free cortisol of 699 nmol/l (range 0-125 nmol/l/24 h), whereas levels of metanephrines, dehydroepiandrosterone, renin and aldosterone were not elevated. At this point, she started on Metyrapone 250 mg 8-hourly as well as hydrocortisone replacement dose, which resulted in an improvement of her glycemic control. The clinical and biochemical findings were discussed in the adrenal multidisciplinary meeting, which advised elective robotic adrenalectomy was made. The surgery was un-eventful with good pos-surgical recovery. Post-surgical histology report was compatible with a multinodular adrenocortical neoplasm, the largest with potentially aggressive behavior (Modified Weiss score: 3/9). Immunohistochemistry showed that the lesion is diffusely positive for inhibin and patchy positive for synaptophysin. Staining for calretinin and chromogranin is negative. MIB1 rate is $<$1%. The follow-up CT scan showed no evidence of recurrence.
Discussion
The radiological features of the lesion were not suggestive of ACC. The Surgical decision was made based on secretory nature of the nodule. It might be advisable to revise the radiological diagnostic criteria in future with emerging new radiological techniques.

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EP109

It hit two targets with one arrow. A case report of Cushing's syndrome as a contributing cause for osteoporosis and thrombosis in a 64-year-old female

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Cushing's syndrome, whether it is ACTH-dependent or ACTH-independent, causes many complications due to chronic exposure of tissues to a glucocorticoid excess. Some of these are arterial hypertension, obesity, osteoporosis, coagulopathies, impaired glucose tolerance and diabetes. We present a case of Cushing's syndrome diagnosed in a 64-year-old female that was referred to the Endocrinology Department from the Physical Medicine and Rehabilitation Department due to multiple vertebral compression fractures and low T score in DXA scan in order to receive anti-osteoporotic treatment. Our patient was known with a history of arterial hypertension grade 3, dyslipidemia, chronic cigarette smoking, lumbar spinal stenosis managed via surgical intervention 3 months prior to our endocrine hospitalisation, left hip arthroplasty, uterine fibroid, intestinal occlusion, multinodular goiter. Physical examination showed an obese patient with central fat distribution, facial and thoracic telangiectasias, high blood pressure, and a systolic murmur. During the screening for endocrine causes of osteoporosis, hormonal tests revealed normal values, except an inadequate supression of 8 am cortisol level after 1 mg overnight of dexamethasone. Subsequent investigations revealed a supressed basal level of ACTH, modified circadian rhythm of cortisol secretion and inadequate supression of cortisol level after 2$\times$2 mg of dexamethasone. Further examinations were made and CT scan showed a mass of 38/35/34 mm in the left adrenal gland with imagistic characteristics suggestive of adenoma. Same CT scan also revealed a pulmonary embolism and massive thrombosis of inferior vena cava. After completion of anticoagulant therapy and remission of thrombosis, left adrenal surgical excision was successfully performed. After this surgical intervention, the patient was initiated with anabolic therapy for severe osteoporosis using a parathyroid hormone analog. The particularity of this case was represented by the cumulative factors leading to both osteoporosis and a procoagulant state. Both postmenopausal status and glucocorticoid excess, as seen in Cushing's syndrome, are contributing to low bone mineral density and osteoporosis. Also, low mobility after previous surgical intervention and hipercortisolism pilled up to coagulation disorders in our patient.

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EP110

Relationship between megaloblastic anemia and ischemic stroke in a patient with adrenocortical carcinoma

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Introduction
The prevalence of megaloblastic anemia in the adult population is poorly documented, but in the elderly, it has been clearly shown that the prevalence of macrocytic anemia increases after the age of 65 years especially in men. The most frequent etiology of vitamin B12 and folate deficiency is malabsorption. They have an action in the conversion of homocysteine to methionine: an increase in homocysteinaemia is currently considered a cardiovascular risk factor. Stroke can result from traditional cardiovascular risk factors, as well as from cancer-induced factors, including hypercoagulability.
Case Report
We report the case of a 65-year-old patient, without any pathological history, diagnosed with a left adrenal cortical mass in the left adrenal space, irregular in shape, fairly well limited, isodense with spontaneous contrast (33UH), measuring 9 cm, with an absolute wash out of 25% and relative to 11%. Associated with an alteration of the general state.With a broken cortisol cycle in the biological assessment with a midnight cortisol level of 12, a negative minute braking and a FU of 4 times normal. The patient presented macrocytic anemia and thrombocytopenia with vitamin B12 deficiency. In our case, the etiology of vitamin B12 deficiency was nutritional deficiency. After 4 days, the patient presented an ischemic stroke of the right middle cerebral artery. The patient was put on anticoagulant treatment and intramuscular hydroxocobalamin treatment at the rate of one ampoule per day for one week, then one ampoule per week for one month, then one ampoule per month continuously. The evolution was marked by an improvement of the anemia and thrombocytopenia and the progressive resumption of the motricity of the left hemisphere and speech. The patient was scheduled for left adrenalectomy after medical preparation.
Discussion
Cobalamin deficiency is common in adults, especially in elderly subjects (more than 20%), but is often unknown or even unexplored, mainly because of frustrating clinical manifestations. Nevertheless, the potential seriousness of its complications, particularly neuropsychiatric, but also hematological, invites to systematically search for it. Moreover the diagnosis of cancer increases the risk of stroke in some cases. This has been found to occur over time after a cancer diagnosis, and is more common in people with cancer.
Conclusion
Hyperhomocysteinemia may be a modifiable risk factor for cardiovascular disease, independent of other risk factors, but its direct causality remains controversial. Megaloblastic anemia associated with a neoplastic context constitutes a criterion for suspicion of thromboembolic pathology or ischemic stroke.

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EP111

Coexistence of adrenocorticotropic hormone-dependent Cushing's syndrome and papillary thyroid carcinoma

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Introduction
Papillary thyroid carcinoma is one of the most prevalent endocrine tumors. Adrenocorticotropic hormone (ACTH) dependent Cushing's syndrome is a rare disease. We report a rare case of coexistence of papillary thyroid carcinoma and ACTH-dependent Cushing's syndrome.
Observation
A 59-year-old man, was admitted to our endocrinology department for exploration of bilateral adrenal incidentalomas discovered in an abdominal CT scan done in the process of exploring portal hypertension. The patient was asymptomatic. The physical examination showed hypertension but no catabolic signs. Hormonal investigation revealed normal methoxylated derivatives plasmatic catecholamines, aldosteronemia and reninemia measurements. Diagnosis of ACTH-dependent cushing's syndrome was made on the basis of lack of plasma cortisol response to low-dose dexamethasone suppression test at 126 nmol/l (above 50 nmol/l) and high plasmatic ACTH levels at 34 pg/ml (above 20 pg/ml). In order to locate the hypersecretion of ACTH (Cushing disease or an ectopic tumor), the patient underwent a High-dose Dexamethasone Suppression test. Cortisol level decreased greater than 50% after 8 mg of dexamethasone, suggesting Cushing disease. Pituitary MRI was normal. Therefore, we performed a body scan that showed a large thyroid nodule. Complementary cervical ultrasound showed an Eu-tirads 5 nodule. Fine needle aspiration was performed but was inconclusive (category III according to the Bethesda system). The patient underwent a total thyroidectomy. The pathological examination identified a papillary carcinoma of the thyroid.
Conclusion
There are few case reports on the coexistence of thyroid papillary carcinoma and ACTH dependent Cushing's syndrome. The co-occurrence of two endocrine tumors with different origins is rare. Common physiopathology must be investigated.

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EP112

Rare etiology of a voluminous adrenal incidentaloma: ganglioneuroma

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Introduction
Ganglioneuroma (GN) is a benign, well-differentiated nerve tumor composed of mature sympathetic ganglion cells and nerve fibers, and most commonly located in the posterior mediastinum and retroperitoneum. GN's are rarely found in the adrenal gland. This tumor is usually asymptomatic and, in the majority of cases, detected incidentally. The diagnostic confirmation is histologic. We report a case of adrenal GN revealed by an adrenal incidentaloma.
Observation
A 50-year-old man, with no history of comorbidities, who consulted for intense left back pain evolving for 4 months. An abdominal CT scan was performed and showed a left adrenal mass measuring 68*83 mm with a spontaneous density of 37UH. An endocrine workup, including urine catecholamine and cortisol levels and a 1 mg overnight dexamethasone suppression test, was normal. Because of the tumor size, A left adrenalectomy was performed, with no related complication. Histological analysis was in favor of a neuroganglioma, no evidence was found for the malignancy. No recurrence was detected during the follow-up visits.
Discussion
GN is a rare benign tumor of neuroectodermal origin, developed from the sympathetic nervous system. It develops along the sympathetic chains, hence its cervical, mediastinal, retroperitoneal or pelvic localization. Adrenal localization is rare. It is composed of mature ganglion cells and a stroma with nerve cells associated with a schwannian contingent, in contrast to neuroblastoma and ganglioneuroblastoma which are composed of more immature ganglion cells with a higher potential for progression. Ganglioneuroma is most often found in children and young adults. The mode of revelation is often incidental, because retroperitoneal ganglioneuromas are usually asymptomatic. However, sometimes abdominal pain, palpation of an abdominal mass, or compression of nearby organs lead to the diagnosis, as in the case of our patient. The treatment remains surgical and consist in the removal of the tumor. The diagnosis of certainty will only be made after a histological study of the surgical specimen. Local recurrence is exceptional, but the possibility of malignant transformation into a ganglioneuroblastoma is possible, which explains the interest of prolonged surveillance.
Conclusion
Ganglioneuroma may sometimes be similar to other adrenal malignancies. Careful evaluation with endocrine tests and imaging procedures is necessary to provide an accurate diagnosis. Definitive diagnosis can be made by histological examination. The prognosis is very good with surgical removal.

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EP113

A case of autoimmune polyglandular syndrome type 2 unmasked after treating subclinical hypothyroidism

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Background
Autoimmune polyglandular syndrome type 2 is an autoimmune disorder that affects many hormone-producing (endocrine) glands. It is characterized by the presence of Addison's disease along with autoimmune thyroid disease and/or type 1 diabetes. The initial presentation can be varied but some patient maybe present with subclinical hypothyroidism and later develop Addisonian crisis. The pathogenesis of Autoimmune polyglandular syndrome type 2 remains unclear, although it may occur due to combination of genetic and environmental factors and affects women more than men. Here we present a patient that who was treated for subclinical hypothyroidism which led to adrenal failure.
Case
46 years Caucasian lady Attended an accident and emergency collapse with a 2-week history of general lethargy and dizziness. She was initially reviewed by her General Practitioner after complaining of tiredness, and weight loss. She had blood tests including a thyroid function test which showed evidence of subclinical hypothyroidism. FT4 16 (pmo/l), TSH 14.70 (Mu/l) She was started on Levothyroxine. 2 months after starting the treatment she became more symptomatic with lethargy and dizzy spells and when she attended Accident and Emergency department she collapses as she was hypotensive BP 80/50. She was given iv fluids, blood test revealed low cortisol of 55. She was started on hydrocortisone initially 100 mg i.m/iv and then 50 mg every 6 hours. Her short synacthen test is below in table 1. A further blood test revealed positive adrenal antibodies. She was discharged home on oral hydrocortisone and fludrocortisone and levothyroxine.
Discussion/conclusion
Subclinical hypothyroidism may be part of polyglandular syndrome Type 2. This consists of hypothyroidism with either adrenal failure or type 1 diabetes. Ruling out adrenal insufficiency is important before starting thyroxine replacement to avoid the life-threatening Addisonian crisis. We recommend carrying out 9 am cortisol followed by a short synacthen test if a 9 am cortisol is low before starting levothyroxine replacement.

Table 1 Short Synacthen Blood test results

Time	Cortisol
9 am	5
9:30 am	5
10 am	5

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EP114

The importance of under-treating adrenal failure in order to allow normal adrenal function following unilateral adrenalectomy for Cushing's syndrome

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A 26-year-old woman presented to the Endocrine clinic with features of Cushing's syndrome (CS). Investigations revealed a non-suppressible cortisol in low dose Dexamethasone suppression test with a suppressed ACTH, and two positive 24-hour urine cortisol collections, indicating CS. CT imaging revealed a left adrenal adenoma of 3.4 cm. Following a left adrenalectomy, she was discharged on once daily Prednisolone 3 mg. She was well for a year except for

one occasion where she reported forgetting to take her Prednisolone and started vomiting. She did not seek medical help. This resolved after she had her Prednisolone dose the following day. On review a year later, a Short Synacthen test (SST), showed a suboptimal response (Table 1). As we were certain that the right adrenal was intact, we planned to gradually reduce the prednisolone dose, to assess for recovery of endogenous cortisol production. Administering a replacement dose of glucocorticoids during the perioperative period helps to preserve normal physiological function, while also reducing potential risks of adrenal crisis. While corticosteroid therapy is commonly used for patients with CS undergoing adrenalectomy, there is no clear consensus on the best approach. A general strategy involves administering steroids both intraoperatively and postoperatively, starting with intravenous administration followed by oral administration, and then gradually tapering the dosage to allow recovery of the HPA axis and endogenous cortisol production. There is limited evidence how best to do this. We have found use of a Prednisolone tapering regimen alongside clinical assessment can help the weaning process. She is currently being weaned down to 1 mg Prednisolone. Patients with adrenal CS have reduced cortisol secretion due to negative feedback on the HPA axis. This leads to a decrease in ACTH release. Reduced ACTH stimulation to both the adrenal cortex surrounding the lesion and the contralateral, often atrophic adrenal gland, results in adrenal insufficiency and need for glucocorticoid replacement therapy. However, patients undergoing unilateral adrenalectomy will have adrenal reserve in the contralateral adrenal gland and should be able to recover endogenous cortisol production. This can be stimulated by deliberately reducing the dose of prednisolone to aid ACTH secretion. Life-long glucocorticoid replacement therapy may be avoided in such patients.

Table 1

Dates & Prednisolone dose	Baseline cortisol 0 minutes (nmol/l)	Cortisol 30 min (nmol/l)	Cortisol 60 min (nmol/l)	ACTH (ng/l)
02/12/22 Prednisolone 2 mg	187	189	218	130
11/10/22 Prednisolone 2 mg	125	137	135	76.4
27/07/22 Prednisolone 3 mg	59	76	81	78.5

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EP115

Adrenal adenomas in untreated Klinefelter syndrome is a frequent finding : Case report

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Introduction
Adrenal adenomas development has been partially explained by aberrant adrenal expression of some hormone receptors. Klinefelter's syndrome is a common cause of hypergonadotropic hypogonadism, which is characterized by increased serum LH level. In this case, we report a patient with Klinefelter syndrome, who was later diagnosed with a non secreting adrenal adenoma.
Case presentation
We report the case of a 57 years old patient, diagnosed with Klinefelter syndrome since the age of 34. He was treated with testosterone replacement therapy for only four years than stopped consulting. The patient was meanwhile treated for hypertension, atrial flutter and heart failure. He also had a history of hypokalemia. He presented to the emergency department for palpitations with dyspnea. Physical examination showed an obesity with BMI at 37.5 kg/m^2. Blood pressure was EKG showed supraventricular tachycardia. Pulmonary embolism was suspected and a CT angiography was conducted, and a right adrenal tumor mesuring 13 mm was discovered. His plasma cortisol level was suppressed to 17 nmol/l after the 1-mg dexamethasone suppression test. Plasmatic normetanephrine and metanephrine levels were normal (respectively 0.52 nmol/l and $<$0.10 nmol/l). His plasma aldosterone concentration and renin activity were 29.9 pg/ml and 3.9 mUI/l, respectively, with a normal aldosterone to renin ratio (17). He was diagnosed as having a non secreting adrenal tumor.
Conclusion
Since untreated Klinefelter syndrome is characterized by increased serum LH, a possible contribution to adrenal tumors development is suggested. It has been described that some patients with untreated Klinefelter's syndrome, later develop primary aldosteronism.

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EP116

Pheochromocytoma associated with von Hippel-lindau disease

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Von Hippel-Lindau (VHL) syndrome is a pathological condition that causes various clinical symptoms and is difficult to diagnose. The most common pathological lesions are hemangioblastomas of the central nervous system, retinal angiomas, renal clear cell carcinomas, and pheochromocytomas. Here we reposrt a case of likely to be VHL due to his family history.
Case
A 33-year-old male suffering from hypertension and a history of hemangioblastoma operated in 2019. The patient had an endoscopic examination after developing nausea, vomiting and weight loss. His endoscopic biopsies include grade 2 neuroendocrine tumors NET). the patient refer to endocrinologist. The father of the patient died at age of 40 due to brain tumor and his brather was operated due to retinal and cerebral hemangioblastoma (in 2013) since that date the familyhad been followed up in the department of neurosurgery with suspicion of VHL. His plasma free metanephrines and urinary metanephrines was high and a computer tomography scan, MIBG and MRI scan of the abdomen showed a solid mass in the lower pole of the lenf kidney at 2.5$\times$2 cm, pancreatic cysts and right adrenal mass at 36$\times$40 laparascopic adrenalectomy and parsiel nefrectomy was performed. The Pathological examination revealed renal cell carcinoma and *pheochromocytomas* with a low PASS score. The contro plasma free metanephrines and urinary metanephrines were withen normal range.
Conclution
Since pheochromocytomas can have low activity, the classical symptoms may be missing. The absence of symptoms can make it difficult to diagnose pheochromocytoma and Even if we couldn't perform the genetic examination there is a strong association between pheochromocytoma and VHL syndrome, and pheochromocytoma is an important feature in the clinical classification of VHL syndrome. The family history of retinal or central nervous system hemangioblastoma (Hb) exists, only one Hb or visceral lesion (renal tumours, pancreatic cysts or tumours, pheochromocytoma, papillary cystadenomas of the epididymis) is required to make the diagnosis of VHL and Due to the risk of pheochromocytoma, the radyologıc sxanning and biochemical tests shoud performed.

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EP117

17 Alpha Hydroxylase Deficiency in congenital adrenal hyperplasia revealed by a ruptured cerebral aneurysm

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Background
A 17 alpha-hydroxylase deficiency (17OHD) is a rare form of congenital adrenal hyperplasia (CAH). Congenital adrenal hyperplasia (CAH) is a group of disorders resulting from defect of one of enzymes necessary for biosynthesis of cortisol.
Case Report
A 33-year-old female suffered from 17OHD. She presented with primary amenorrhea, lack of secondary sexual characteristics, and hypertension complicated by ruptured cerebral aneurysm. Laboratory tests showed hypokalemia, low levels of androgens, corticosteroid, and high levels of adrenocorticotropic hormone, 11 Deoxycorticosterone and progesterone. Due to the severe initial presentation with signs of malignancy in adrenal imagery, the decision was to realize left adrenalectomy and to discuss the primary amenorrhea previously. The clinical manifestations, imaging and laboratory results appeared to be consistent with a diagnosis of CAH in the patient, due to the observed 17α hydroxylase deficiency. The patient is putted on corticosteroids (dexamethasone) with normalization of adrenocorticotropic hormone, normal kaliemia and blood pressure.
Discussion
The classical presentation of 17OHD is hypertension,hypokalemia, and delayed puberty with lack of secondary sexual characteristics in a female of pubertal age group. Our patient had all the classical features. The diagnosis of 17OHD is based on clinical, biochemical, and molecular features. In our case, biochemically, there were decreased concentrations of DHEA, androstenedione, testosterone,

estradiol, and cortisol, and increased concentrations of 11 Deoxycorticosterone and ACTH.
Conclusion
17OHD is a rare disease associated with primary amenorrhea and hypertension. This case shows the importance of vital signs measurement, medical history and commitment to a systematic approach.
KeyWords: adrenal hyperplasia- 17 alpha hydroxylase-congenital-deficiency-steroids

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EP118

Coexistence of Gilbert's disease, thyroid nodule, parathyroid adenoma, and Cushing's syndrome: A rare presentation

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Introduction
Gilbert syndrome is a common autosomal dominant hereditary condition characterized by intermittent unconjugated hyperbilirubinemia in the absence of hepatocellular disease or hemolysis. Multiple endocrine neoplasia (MEN) is defined by the association of a neoplasia or hyperplasia of at least two endocrine glands and caused by multiple mutations. Rare cases of atypical MEN were reported in the literature. We report the case of a patient with a history of gilbert's disease, toxic thyroid nodule and primary hyperparathyroidism who was found to have Cushing's syndrome
Observation
It is a 60-year-old man, diagnosed at the age of 37 with Gilbert's disease revealed by a jaundice. At that time, an hyperthyroidism due to a toxic thyroid nodule was diagnosed and treated by surgery. At the age of 42, he was diagnosed with primary hyperparathyroidism (calcemia = 2.77 mmol/l, PTH = 148 pg/ml) caused by a left lower parathyroid adenoma. He underwent a parathyroidectomy. During the work-up for multiple endocrine neoplasia, a 2 cm left adrenal nodule was discovered on an adrenal scan. Initial investigations had revealed a non-secreting adenoma and regular surveillance was carried out. Given the later appearance of hypertension and hypokalemia, a hormonal evaluation was performed again. The results of the hormonal investigation revealed normal levels of methoxylated derivatives of plasmatic catecholamines, as well as normal levels of aldosterone, renin, and the aldosterone-renin ratio in the plasma. However, blood cortisol after a Low-dose Dexamethasone Suppression Test was elevated at 137 nmol/l and ACTH levels was high (86 pg/ml). Diagnosis of ACTH-dependent Cushing's Syndrome was retained. MRI of the pituitary gland revealed an arachnoid cyst. Body scan did not show any abnormalities.
Conclusion
Gilbert's disease, toxic thyroid nodules, parathyroid adenoma, and Cushing's disease are all separate medical conditions that may have different causes, symptoms and treatments. It is possible that they can be associated in some cases, but we could not confirm whether the patient had this multiple endocrine dysfunction as a coincidence or they had a common etiology.

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EP119

Intermittent cushing's syndrome: diagnostic challenges

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Introduction
Cushing's syndrome (CS) is typically characterized by faciotronic obesity with signs of protein hypercatabolism, which may be iatrogenic or endogenous (adrenal or ATCH dependent). We report a case of CS of unusual presentation.
Case Report
We report the case of a 45-year-old patient, referred for etiological assessment and management of an atypical cushing syndrome.
– Symptomatology dates back to 2007, by the appearance of abdominal pain with vomiting and asthenia treated as acute adrenal insufficiency.
– The exploration was then completed by the realization of a biological assessment of the adrenal cortex (17 total urinary cetosteroids = 3.95 mg/24 h (normal between 4.9 and 14)), and a radiological exploration made of thoraco-abdominal CT scan and pituitary MRI: without abnormalities.– In addition, the patient reports the appearance since 2007 of facial erythrosis, skin fragility, with progressive weight gain, with stretch marks and asthenia, evolving intermittently, this symptomatology complicated 3 months ago by the worsening of the intensity, significant asthenia, muscle weakness, myalgias, muscle cramps, spinal bone pain, hair loss, with erythematosquamous lesions and ecchymosis more evident at the level of the MI, no melanoderma, no acne, no seborrhea.
– Urinary free cortisol was 50.7 μg/24 h, with an 8-hour cortisol level of 6.4 μg/dl.
– No other signs of pituitary insufficiency or hypersecression werw reported.
– For confirmation of cushing's syndrome: Braking not done (because of IS), CLU not done (patient under hydrocortisone), cortisol cycle was performed (no disruption of the circadian cycle).
– Etiological workup: Biological: hypophysogram:ACTH = 2.96, hypogonadotropic hypogonadism. Radiological: adrenal CT scan(no abnormalities), octreoscan (no abnormal fixation in favor of ectopic cushing), brain MRI (arachnoidocele pushing back the pituitary gland).
Discussion
Diagnostic hypotheses: This is most likely a cushing's disease with an apoplectic pituitary adenoma responsible for arachnoidocele, in view of the progressive onset of intermittent cushing's syndrome, hypogonadism of central appearance, and the negativity of the rest of the workup although the ACTH is low that can be explained by braking of the corticotropic axis by CTC in the long term (equivalent of 7.5 mg of prednisone for 12 years).
Conclusion
This case illustrates an atypical and confusing presentation of CS highlighting the clinical polymorphism of this disease and the resulting diagnostic difficulties.

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EP120

Primary Aldosteronism and Cortisol Cosecretion in a Patient with Adrenal Adenoma

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Background
Primary aldosteronism (PA) is a group of disorders characterized with inappropriately high adrenal aldosterone production, suppressed renin and hypertension. Prevalence of PA is approximately 5-10% in people with hypertension and up to 20-50% in those with resistant hypertension. PA is associated with increased cardiovascular and cerebrovascular morbidity and mortality rates compared with patients with essential hypertension when matched with age, sex and blood pressure. PA is commonly caused by an adrenal adenoma, unilateral or bilateral adrenal hyperplasia (BAH), or in rare cases adrenal carcinoma or inherited conditions of familial hyperaldosteronism. The cause of PA dictates the optimal treatment strategy- curative surgery (unilateral adrenalectomy) or mineralocorticoid receptor blockade. Corticotropin (ACTH)-independent hypercortisolism is relatively rare condition, diagnosed in <5% of patients with adrenal tumors or hyperplasia, while mild autonomous cortisol secretion (MACS) is common, affecting up to 50% of patients with unilateral adrenal adenomas. ACTH independent hypercortisolism can present with overt features of Cushing Syndrome (CS) or as MACS. Laparoscopic adrenalectomy is the treatment of choice.
Case presentation
We present a case of a 45 year old man with 10 year history of hypertension and spontaneous hypokalemia first documented 5 years ago. He was treated with Perindopril, Amlodipine, Indapamide, Nebivolol and potassium supplements. Laboratory workup planned at our clinic confirmed the diagnosis of primary aldosteronism. Adrenal CT revealed 14 mm left adrenal adenoma (-20 HU). Further evaluation with dexamethasone suppression test, ACTH and DHEA-S confirmed MACS. Considering the cosecretion of cortisol with aldosterone, adrenal venous sampling (AVS) was no longer required and the patient was advised about unilateral adrenalectomy.
Conclusion
In conclusion, in patients with large aldosterone-producing adenomas, the possibility of MACS should be evaluated as the identification of aldosterone and cortisol co-secreting neoplasms will require specific approach.
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EP121

Cushing's disease in children: about a case

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Cushing's disease (CD) is rare in paediatric practice but requires prompt investigation, diagnosis and therapy to prevent longterm complications. We report the case of a young 12-year-old patient who presented with probable Cushing's disease complicated on the bone level by osteopenia. Cushing's syndrome seems to have been evolving for 2 years, i.e. at the age of 10, manifesting itself by a weight gain of 20 kg in 18 months. Clinically, she presents clear signs of hypercortisolism with faciotroncular obesity, large and colored stretch marks and amyotrophy of the lower limbs. The biological exploration returns in favor of an ACTH-dependent Cushing syndrome. Endogenous hypercortisolism was confirmed by a negative weak braking test on plasma and urinary cortisol and etiologically ACTH is high confirming ACTH-dependent hypercortisolism, strong braking on plasma and urinary cortisol is positive in favor of of hypothalalmohypophyseal origin. The hypothalamic-pituitary MRI does not find any pituitary adenoma but highlights a small cystic formation with sediment in hyposignal, evoking a Rathke's pouch cyst. The cervicothoraco-abdominal scanner is without anomalies. Catheterization of the inferior petrous sinuses showed a Centro peripheral gradient without lateralization. The diagnosis of CS has remained a challenge in clinical practice, with limited sensitivity and specificity of laboratory and imaging tests. For this reason clinical examination, and sometimes long-term observation, can be key to correct diagnosis.

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EP122

Primary Aldosteronism due to Adrenal Adenoma

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A patient, 24 y/o male, presented with the regular occurrence of severe hypertension for past two years: 150-170/100 mmHg. He complained of occasional vertigo, fatigue, and rare muscle cramps. The laboratory findings showed marked hypokalemia–2.7 mmol/l. Thyroid function tests, creatinine, magnesium levels were normal. Heart US showed septal thickening. He had been taking spironolactone 50 mg/day according to the prescription of his cardiologist for the last 2 weeks. Based on patient's history, clinical presentation, and lab findings, primary aldosteronism was suspected. We recommended withdrawing spironolactone and temporarily replacing it with verapamil and measuring the levels of aldosterone and renin in 4 weeks after withdrawal. The levels of aldosterone and renin were measured after a month of withdrawal of spironolactone. Renin levels were completely suppressed: <1 ng/l (normal range 1.7-23.9 ng/l), and the aldosterone/renin ratio was markedly increased: >218. Aldosterone levels were borderline elevated: 218 ng/l (normal range 11.7-236 ng/l), probably due to hypokalemia which could not be fixed even with a high-dose potassium therapy. We did not conduct confirmatory tests as diagnosis of primary aldosteronism was evident. The CT scan with contrast was performed that revealed 1 cm adenoma in the left adrenal gland. Due to patient's young age, presence of hypertension, hypokalemia and high aldosterone/renin ratio, the diagnosis of Conn's syndrome (primary aldosteronism caused by aldosterone-producing adenoma) was indubitable. AVS was not recommended. The patient had been prepared for surgery with 50 mg spironolactone therapy. His potassium was normal and blood pressure normalized after 2 weeks of spironolactone therapy. A laparascopic adrenalectomy was performed in September 2022. Spironolactone was withdrawn after the surgery. Potassium level in blood in two weeks postoperatively was 4.7 mmol/l, blood pressure decreased (120/75 mmHg to 130/90 mmHg). Prompt improvement in blood pressure indicates that most probably he had short duration of aldosteronism and process was completely reversible. He was recommended to monitor his blood pressure regularly without any additional treatment.

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EP123

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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Introduction
Congenital Adrenal Hyperplasia (CAH) are any of several autosomal recessive diseases resulting from mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids, glucocorticoids or sex steroids from cholesterol by the adrenal glands (steroidogenesis).
Case Report
We describe a case report of a 20 year-old female with congenital adrenal hyperplasia (CAH). The 20-year-old female patient was born with genital ambiguity. She was brought up as a girl. Karyotype test result was 46,XX, and laboratory examination showed a high value for 17-hydroxyprogesterone 17OHP (259.4 ng/ml ng/ml), and Dehydroepiandrosterone sulfate (9136 ng/ml) with elevated adrenocorticotropic hormone ACTH (377 ng/l). MRI examination showed atrophic uterus and ovaries. Computed adrenal tomography showed and increased bilateral adrenal glands. The examinations were consistent with the diagnosis of adrenal hyperplasia due to 21 hydroxylase deficiency. The patient is putted on corticosteroids (Oral hydrocortisone) and antiandrogens .The hormonal monitoring showed efficiency of treatment(Decreased 17OHP, DHEA S, ACTH and testosterone).
Discussion
The majority of virilized 46,XX infants will prove to have CAH. CAH is also the most common disorder of sex development. Simple virilizing 21-hydroxylase deficiency is usually diagnosed in female patients shortly after birth owing to genital ambiguity (CYP21 mutation). Mild forms of 21-hydroxylase deficiency in females are identified later in childhood due to precocious pubic hair, partial or complete fusion of labioscrotal folds, and phallus enlargement to clitoromegaly, and are often accompanied by accelerated growth and skeletal maturation due to excess and postnatal exposure to adrenal androgen, either not treated or inadequately treated. 46,XX CAH is a rare case. Management of the patient is based on substantial examination, and the patient's preference has an important role in deciding the type of treatment. In this case, all examinations were consistent with a diagnosis of CAH and the patient has a tendency to identify as female so the operation (clitoroplasty) will be done.
KeyWords: 21Hydroxylase -Deficiency-Adrenal Hyperplasia
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EP124

Young man with back pain, is it Cushing's

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Introduction
Cushing's syndrome is rare disease with annual incidence 2/ million. It carries a high mortality rate if untreated. ACTH independent Cushing's with Adrenal adenoma is responsible for 10% of cases. This is a case of a young gentleman with back pain, vertebral fracture, in presence of left adrenal incidentaloma, normal MRI pituitary, and hormonal profile indicative of possible non-detectable central pituitary lesion, diagnosis of likely adrenal Cushing's was established. Left adrenalectomy was performed with smooth recovery, histopathology has confirmed a benign nature of adrenal adenoma.
Case presentation
37-year-old gentleman presented in A&E with chest pain, radiating to the back. PMH: hypertension on triple therapy. Family history: non-significant In view of chest pain, he had a CT Aortogram to rule out aortic dissection, this showed left adrenal incidentaloma and T7 vertebral body collapse. In view of left adrenal mass and vertebral fracture he had further investigations to rule out cortisol excess. At this point overight dexamethasone suppression test was arranged.
Investigations
CT angiogram: left adrenal mass 3.4 cm, 5 HU likely benign adenoma. MRI Spine: subacute **T 7 vertebral** body fracture. **FSH 7.9** U/l **LH 3.7** U/l **Testosterone 5.3** nmol/l. Normal Prolactin, Thyroid, IGF1 and random cortisol. In view of left adrenal mass, he was referred to Endocrine clinic. Ongoing vision disturbance and weight gain was reported. On Examination: BP 137/69 BMI 35.9, evident abdominal striae. He failed to suppress high dose overnight dexamethasone suppression test. [cortisol 123 nMol/l with ACTH 19 (0-46 ng/l)], and low dose dexamethasone suppression test [(72 nMol/l with ACTH 9)]. Bone densitometry: Lumbar spine Osteopenia **T-score -1.9 Z-score -1.8**. Elevated UFC (107 nmol/l), and UFC excretion index (25 nmol/24 hours). MRI pituitary: normal.
Differential Diagnosis
1.Established Cushing's disease diagnosis with possible left adrenal driven etiology. 2.On the other hand, he had inappropriately low FSH and LH for an

extremely low testosterone level, and his ACTH was not suppressed. There is a possibility of small pituitary adenoma which is non-detectable on pituitary MRI.
Treatment
1. Metyrapone
2. laparoscopic left adrenalectomy
Outcome
Metyrapone was stopped and his post-operative low dose dexamethasone suppression test confirmed his Cushing's has now been cured. Histopathology: benign adrenal adenoma. Reduced anti-hypertensive medications to one medicine
Future Plan
1. Blood pressure and osteopenia monitoring - expected to improve.
2. Monitor for possible post-operative corticotrope tumor growth and adrenal insufficiency.
3. Gonadotrophin and testosterone re-assessment.
4. Genetic test to rule out MEN.

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Calcium and Bone

EP125

Application of untargeted metabolomics in primary hyperparathyroidism

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Background
The excessive secretion of parathormone by parathyroid glands is a common disorder known as hyperparathyroidism. With a prevalence of 0.1-0.4 percent in the general population and 2-4 percent in post-menopausal women, primary hyperparathyroidism is the third most frequently reported endocrine disorder. According to estimates, the prevalence of primary hyperparathyroidism has escalated in recent years, probably due to the increasing rate of parathormone and calcium measurements. Evaluation of whether patient with hyperparathyroidism requires parathyroidectomy assumed important place in endocrinology practice. Metabolomics is a relatively new field of science serving a source of novel potential biomarkers. This new important 'omic' approach delivers biochemical information associated with the regulation of specific gene transcripts.
Objective
The aim of the study was to explore metabolic differences in plasma metabolome between patients with primary hyperparathyroidism and healthy individuals.
Methods
A retrospective, single-center study was performed on 28 patients with primary hyperparathyroidism and 30 healthy volunteers. Two complementary liquid-phase separation methods, capillary electrophoresis combined with TOF (CE-TOF-MS) and liquid chromatography coupled with QTOF (LC-QTOF-MS), were used to obtain metabolic fingerprints of plasma samples. A filtering and QA procedure, followed by uni- and multivariate analysis were applied to the acquired data. All included patients underwent the endocrine work-up aimed to study the hormonal and electrolyte status of primary hyperparathyroidism.
Results
Untargeted metabolomics has been successfully applied to track differences in plasma metabolome between PHPT patients and healthy subjects regardless of the technique used. The application of two complementary liquid-phase separation methods significantly increased metabolite coverage. The observed differences in metabolic profiles were subtle but amounted to more than 250 metabolic features: 36 CE/MS, 91 LC/MS for pos mode, and 127 LC/MS for neg mode. More than 20% of noted features were steroid hormone sulfates and vitamin D3 derivatives.
Conclusions
The most significant differences were observed between anionic metabolites detected by LC-MS, followed by cationic compounds measured by CE-MS, while the weakest differences were observed for cationic molecules detected via LC-MS. Presented results show that application of untargeted metabolomics in patients with primary hyperparathyroidism may help to understand the pathogenesis of primary hyperparathyroidism and to discover new biomarkers in easy-to-obtain biological samples. However, a larger cohort is necessary to search for potential biomarkers due to subtle changes in the levels of metabolites in patients with primary hyperparathyroidism.

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EP126

Diagnostic efficiency of the fine needle aspirate parathyroid hormone assay in parathyroid adenomas

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Objective
Evaluate the utility of analytical determination of parathyroid hormone assay in fine-needle aspirate as a diagnostic test for parathyroid adenoma in patients with primary hyperparathyroidism.
Material and Methods
retrospective observational study of 58 patients diagnosed with primary hyperparathyroidism in our hospital who underwent ultrasound-guided FNA of lesions compatible with parathyroid adenoma with determination of PTH in fine-needle aspirate (PTHL). A cut-off point for PTHL of 100 pg/ml was considered positive.
Results
70.7% of the sample was female and the mean age was 59.2 ± 13.3 years. Fifty-eight lesions were punctured with a mean diameter of 12.78 ± 11.55 mm, and no procedure-related complications were recorded. Sestamibi-Tc99m gammagraphy showed no uptake in 85.9% of cases, intra-thyroid adenoma was suspected in 8.6% of cases and in 74.1% there was discordance between localization tests (ultrasound, gammagraphy, 4D parathyroid CT). The mean PTH_L value was 3399.7 ± 7776.2 pg/ml, and 74.1% of cases were considered positive. Until the analysis was performed, 31 patients had undergone surgery and the result of the surgery was concordant with the localised lesion by PTHL in 83.9% of the cases. The determination of PTHL ($\geq$ 100 pg/ml), in our series, has a sensitivity of 93%, a positive predictive value of 100%, a specificity of 100% and a negative predictive value of 60%. Two false negative cases were observed with PTHL values of 9 and 72 pg/ml.
Conclusion
PTH measurement in FNA aspirate is an affordable and useful diagnostic test to confirm the location of parathyroid adenoma. Further studies are needed to establish a standardised cut-off point for PTHL. This technique could be established as a complementary or safe alternative test in cases with difficult localisation or discordant localization tests.

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EP127

Key factors associated with impaired glucose metabolism in primary hyperparathyroidism

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Background
Primary hyperparathyroidism (PHPT) can present with not only classic complications like bone and kidney pathology but also with different metabolic disorders and cardiovascular diseases. The prevalence of diabetes mellitus type 2 (DM2) in patients with PHPT is higher than in general population but the mechanism of carbohydrate metabolism alteration in PHPT remains unclear.
Aim
The aim of this study is to estimate parameters associated with impaired glucose metabolism in patients with PHPT using a method of machine learning–decision tree.
Material and Methods
The study included clinical data of 307 patients with PHPT. None of the included patients received drugs that affect mineral metabolism. We assessed age, PHPT duration, the presence of prediabetes or DM2, serum calcium, phosphorous, iPTH, osteocalcin levels, BMI. Decision tree (DT) is a classic supervised machine-learning method used for solving classification problems. DT consist of decision nodes and end nodes. Decision nodes contain decision rules, end nodes–value of target variable with Gini index characterized quality of classification. DT was built in Python using library Scikit-learn. The Bayes theorem was used to determine the conditional probability of impaired glucose metabolism in PHPT.
Results
55 patients with PHPT had prediabetes/DM2 (17.9%). They were older (60 [55;70] vs 58 [50;66] years, $P = 0.011$), had higher BMI (32.7 [28.1; 39.4] vs 27.2 [24.2; 30.4] kg/m^2, $P < 0.001$) and lower serum osteocalcin levels (33.1 [20.8; 51.8] vs 48.1 [34.0; 76.3] ng/ml, < 0.001) compared to those without carbohydrate metabolism disorders. Thus, DT was built using these parameters (age, the presence of obesity, osteocalcin

level). To form a decision rule, a terminal leaf node with the prevailing class 1 (presence of prediabetes/DM2) and the lowest Gini index were identified. The absence of obesity in combination with osteocalcin >36.8 ng/ml in patients with PHPT was less often associated with impaired glucose metabolism (OR = 0.04, 95% CI [0.01-0.17]). Vice versa, obesity with osteocalcin level ≤ 36.8 ng/ml can be the potential marker of hyperglycemic state in PHPT. The probability of carbohydrate metabolism disorders in such patients is 19.8%.

Conclusion

Patients with PHPT and obesity with osteocalcin level less than 36.8 ng/ml should be considered as the risk group of prediabetes and DM2. In such patients extensive evaluation of carbohydrate metabolism is preferred.

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EP128

Height loss is almost 5 times more correlated with trabecular bone score than with bone mineral density. Study on over 900 patients (2023)

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Aim

To show that height loss is more correlated with vetebral micoarchitecture than with Bone Mineral Density (BMD).

Material and Method

A. DEXA: made with a GE-Lunar Prodigy Pro # 500074. Vertebral microarchitecture was investigated by Trabecular Bone Score (TBS). TBS software: TBS iNsight®, version 3.0.2.0.

B. Patients. 902 patients, 844 (93.6%) women, 58 men. Only 42 under 50 years. Age average: 65.79 years. Women: 65.56 years, men 69.15 years.

C. Height measurement. At the time of DEXA analysis, each patient's height was measured (centimetres). Patients were asked to appreciate the difference in height compared to a previous age to which they can relate.

D. Statistical analysis. Student tα test was used for differences. Linear correlation test (r) was used for correlations.

Results

1. Diagnosis of osteoporosis. BMD scores led to the classic diagnosis of osteoporosis (score $<$ -2.5) in only 28.38% of patients. TBS T scores suggested the diagnosis of osteoporosis in 71.95% of patients (Table). The concordant diagnosis of osteoporosis by the intersection of BMD and TBS scores occurred in only 24.06% of patients.

2. Decreasing height. a. Average: 3.58 cm. Women loss height = 3.58 cm, Men loss height = 3.41 cm. Individual maximum loss was 12 cm (woman, 66 y). Average maximun loss at 8th decade = 7.5 cm. Minimum mean loss was at <45 years = 0.8 cm. **b. Correlations between height decrease and DEXA values.** The correlation of the decrease in height with BMD T score was "r" = 0.0724, $P<0.05$. The correlation of height decrease with TBS was r" = 0.3592 $P<0.001$. The value "r" for the correlation with TBS was 4.96 times higher.

Conclusions

1. Vertebral compression is correlated with age, higher in women than in men.

2. Patients lose up to 12 cm, beginning with the 6th decade of life, maximum average in 8th decade.

3. TBS is more correlated with vertebral microarchitecture and decrease in height with age compared to BMD, since the correlation "r" between TBS values and height decrease vs the correlation between height decrease and BMD is almost 5 times higher.

		BMD-T score			
		Normal	Osteopenia	Osteoporosis	Total
TBS-T score	Normal	35	12	5	52
		3.68%	1.33%	0.55%	5.76%
	Partial degraded - 1–2.5 (osteo-penia)	75	92	34	201
		8.31%	10.2%	3.77%	22.28%
	Degraded $<$ -2.5 (osteo-porosis)	143	289	217	649
		15.85%	32.04%	24.06%	71.95%
	Total	**253**	**393**	**256**	**902**
		28.05%	43.57%	28.38%	100.0%

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EP129

Prediabetes is associated with lower trabecular bone score (TBS): Comparison of TBS according to the prediabetes phenotype

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Objective

Diabetes mellitus (DM) is known to be associated with a lower trabecular bone score (TBS) and an increased risk of fracture. However, little is known regarding whether it is associated with poor bone results in pre-diabetic individuals. Despite the fact that both IFG and IGT are characterized by insulin resistance and β-cell dysfunction, the metabolic abnormalities are quite distinct between the two disorders. Impaired fasting glucose (IFG) was marked by dysfunctional insulin secretion and decreased hepatic insulin sensitivity. In contrast, impaired glucose tolerance (IGT) was related with decreased whole-body insulin sensitivity, followed by a decline in β-cell function. We examined if TBS differed depending on the prediabetes phenotype.

Methods

This was a cross-sectional analysis of baseline data collected from 30- to 64-year-old participants in the Study of the Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) Cohort Study. A whole-body dual-energy X-ray absorptiometry (DXA) scan and an oral glucose tolerance test were performed. Excluding those with diabetes, liver cirrhosis, chronic kidney disease, or cancer, as well as those on osteoporosis drugs, steroids, or thyroid hormones, or who had ever received hormone replacement treatment, we enrolled 3.276 individuals. Subjects were classified as having normal glucose tolerance (NGT), isolated IFG, isolated IGT, or combined IFG and IGT (IFG + IGT). Statistical analyses were conducted by dividing into three groups (male, premenopausal women and postmenopausal women).

Results

Males with isolated IGT exhibited a lower TBS after adjusting for age, weight, vitamin D, Hba1c, cigarette smoking, and alcohol intake (1.466 vs 1.494, $P=0.040$). However, statistical significance disappeared when visceral fat was additionally adjusted for. In premenopausal women, patients with isolated IFG had a lower TBS than those with NGT (1.493 vs 1.513, $P=0.044$), and statistical significance was preserved even after visceral fat was further adjusted. There were no significant differences in TBS among groups of postmenopausal women.

Conclusion

Similar to diabetics, prediabetics have decreased TBS levels compared to NGT people. However, there were gender disparities in the association between TBS and prediabetes. Insulin resistance with visceral fat may have a greater impact on TBS in men, but disruption in insulin secretion may have a greater impact on TBS in premenopausal women.

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EP130

Tension-free thyroidectomy (TFT) with medial approach to the recurrent laryngeal nerves and parathyroid glands helps to achieve a low rate of permanent postoperative hypoparathyroidism

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Background

Hypoparathyroidism is one of the most important complications of total thyroidectomy. Its treatment with the use of recombinant parathyroid hormone (PTH) is limited now, therefore the prophylaxis of post-surgical hypoparathyroidism is very important. A method of tension-free thyroidectomy (TFT) was proposed in 2021. TFT uses unusual medial approach to the recurrent laryngeal nerves (RLN) and parathyroid glands (PG), together with several principles decreasing traction applied by the surgeon to these anatomical structures.

Method

117 consecutive patients underwent total thyroidectomy with the use of TFT technique (there were 468 PGs at risk). In 46 (39.3%) cases patients additionally underwent central neck dissection with preservation of the thymus horns and their blood supply, in 13 cases–lateral neck dissection. Indications for surgery were thyroid cancer ($n=56$; 47.9%), follicular neoplasia ($n=25$; 21.4%), Grave's disease ($n=27$; 23.1%), nodular toxic goiter ($n=7$; 5.9%), nodular nontoxic goiter ($n=2$; 1.7%). Mean thyroid volume was 69 ml ($\pm$58 ml). Mean diameter of the thyroid nodule was 42 mm ($\pm$64 mm). Intraoperative neuromonitoring was

used in all the cases (5 mV). Calcium and PTH levels were measured on the day of surgery and on the day 1. In cases where PTH level dropped, additional calcium and PTH tests were performed on the 14th, 30th, 90th postoperative days. Laryngoscopy was used in all the cases prior and after surgery to evaluate vocal folds mobility.
Results
Unintentional complete PG removal occurred in 1 case (0.2% of PGs at risk), a fragment of parathyroid tissue was unintentionally removed in 14 cases (3.0% of PGs at risk). Hypoparathyroidism occurred in 12 patients (10.2%). In 7 out of these patients PTH level started to rise on the first postoperative day. In all the cases PG function has restored in the next 90 days, thus the rate of permanent hypoparathyroidism was 0%. Only in 2 cases hypoparathyroidism occurred in patients with unintentionally removed PG fragments, which means that the main reason for hypoparathyroidism was ischemia. An additional benefit of TFT was the low rate of RLN palsy which was registered in 2 cases (unilateral palsy; 0.9% of 234 RLNs at risk). In both cases RLN function restored, therefore the rate of permanent RLN palsy was 0%.
Conclusion
This initial study shows that TFT gives an opportunity to achieve the low rate of permanent complications such as hypoparathyroidism and RLN palsy.

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EP131

Hypercalcemic hyperparathyroidism after bariatric surgery–primary or tertiary? Case report

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Bariatric surgery significantly reduces obesity-related comorbidities. Secondary hyperparathyroidism (SHPT), due to calcium malabsorption and vitamin D deficiency, has been frequently reported, however, in patients after bariatric surgery. Whether chronic SHPT after bariatric surgery could ultimately evolve into tertiary hyperparathyroidism has not been clarified. Here, we report a 59-old-woman who presented with osteoporosis (T score at the lumbar spine -4.1 and T score at the distal radius -2.5). Mild primary hyperparathyroidism (PHPT) was documented in the laboratory work up: total calcium 2.65 mmol/ l (normal ranges 2.15-2.55 mmol/l) and parathyroid hormone (PTH) 8.9 pmol/l (normal ranges 1.58-6.03 pmol/l). MIBI scintigraphy revealed a left upper enlarged parathyroid gland which was removed. Histopathology was reported as parathyroid hyperplasia. Postoperatively, hypercalcemia persisted. The patient then underwent PET-CT with fluorocholine which showed weak activity in the left lower parathyroid gland. An enlarged parathyroid gland was not, however, found during the second surgery. The patient underwent left hemithyroidectomy to remove a potential intrathyroidal parathyroid gland but none was seen on postoperative histopathology and hypercalcemia continued. The patient had a history of laparoscopic gastric banding for obesity 10 years prior to her presentation with PHPT. To reduce hypercalciuria and to improve calcium absorption, hydrochlorothiazide and vitamin D supplementation were started, followed by oral ibandronate. After a year of treatment bone mineral density at the lumbar spine significantly improved (by 22%) whereas serum calcium and PTH have not changed. Although we do not have a histologic correlate, a combination of inaccurate parathyroid imaging, multiglandular parathyroid disease and complicated parathyroid surgery together with a significant bone mineral density improvement might be indirectly suggestive of tertiary hyperparathyroidism in a patient with a history of bariatric surgery. Longstanding SHPT may contribute to the development of hypercalcemic, i.e. tertiary, hyperparathyroidism. In a patient presenting with hypercalcemic hyperparathyroidism and a history of bariatric surgery, multiple parathyroid gland disease with tertiary hyperparathyroidism should be considered. Supported by MH CZ - DRO (Institute of Endocrinology - EÚ, 00023761).

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EP132

Comparison of the prediction powers of hypercalciuria tests for nephrolithiasis in patients with asymptomatic primary hyperparathyroidia

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Objective
One of the ways to predict nephrolithiasis,which is one of the surgical indications in patients with asymptomatic primary hyperparathyroidism,is to detect hypercalciuria.A calcium excretion of >400 mg/day in 24-hour urine, >4 mg/kg/day calcium excretion in 24-hour urine or a fractionated calcium excretion (FECa) >0.010 guide us in the detection of hypercalciuria and therefore nephrolithiasis.The aim of our study is which of these three tests is more useful in predicting nephrolithiasis and therefore in determining the indication for surgery in asymptomatic patients.
Materials and Methods
Biochemical examinations and imaging methods records of patients diagnosed with primary hyperparathyroidism ($n=271$) at Dokuz Eylul University Hospital Endocrinology and Metabolic Diseases Department between 2016-2022 were retrospectively analyzed and the predictive power of the aforementioned hypercalciuria screening tests for nephrolithiasis was compared.
Results
Median age at diagnosis was 56,adjusted calcium 10.9 mg/dl,estimated glomerular filtration rate 95 ml/min, 25-OH (hydroxy) vitamin D 17 ng/ml,phosphorus 2.8 mg/dl,parathormone 156 pg/ml,adenoma size (maximum) 12 mm and fractionated calcium excretion was 0.016 of the patient included in our study. There was no significant difference in adjusted calcium, phosphate, parathormone and 25-OH vitamin D levels between patients with and without nephrolithiasis.A significant difference was found in terms of median age at diagnosis,urinary calcium and fractionated calcium excretion. There was a significant difference between categorical variables in terms of urinary calcium >400 mg/day and urinary calcium >4 mg/kg/day. According to univariate analysis results, phosphorus ($P=0.017$), 24-hour urinary calcium ($P=<0.05$), urinary calcium >400 mg/day ($P=0.002$),urinary calcium >4 mg/kg/day ($P=0.003$) and fractionated calcium excretion ($P=0.005$) were significant in terms of nephrolithiasis.According to the results of univariate analysis,we determined that male gender increased the probability of nephrolithiasis by 2 times.It was determined that low phosphorus increased the probability of nephrolithiasis 1.8 times, urinary calcium excretion >400 mg/day 3.2 times,urinary calcium excretion >4 mg/kg/day 2.3 times and fractionated calcium excretion 16.3 times. According to the results of multivariate analysis,we found that fractionated calcium excretion ($P=0.007$) was significant in terms of nephrolithiasis and it was found that it increased the probability of nephrolithiasis 20.7 times.There were no significant findings in terms of gender,age at diagnosis, adjusted calcium,phosphorus,estimated glomerular filtration rate and parathormone.
Conclusions
As a result of our study,all three hypercalciuria tests were found to be significant in terms of predicting nephrolithiasis.However,the most valuable of these tests,which is also the aim of our study,was found to be fractionated calcium excretion.

Keywords: Primary Hyperparathyroidism,Hypercalciuria,Nephrolithiasis
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EP133

The Russian Registry of primary hyperparathyroidism, the latest update

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Introduction
Primary hyperparathyroidism (PHPT) is one of the most common endocrine disorders. No major epidemiological research has been previously conducted in the Russia. This served as the basis for the creation of the Russian online registry of PHPT with accessibility from various regions of the country.
Aim
Aim of this study was to estimate the clinical profile, surgical and medical therapy of the patients with different forms of PHPT.
Material and Methods
The cross-sectional, observational study was carried out at the Endocrinology Research Centre (Moscow,). The present study explored retrospective data from 6003 patients submitted to the Registry between 12.12.2016 and 25.10.2022 (http://pgpt.clin-reg.ru/) from 81 regions of the Russia.

Results
The median age was 59 [60; 66] years with a female: male ratio of 11.7:1. Symptomatic PHPT was observed in 73.5% of patients while asymptomatic form - in 26.5%. The predominant clinical manifestation was the combination of skeletal and renal complications (41.7%), while isolated disorders were noted in 35.9 and 22.4%, respectively. There was a difference between symptomatic and asymptomatic patients in age (60 [53; 67] vs 54 [45; 62] years, $P<0.001$). Serum iPTH, albumin adjusted and ionized Ca levels were higher in symptomatic patients ($P<0.001$ for all), hypophosphatemia was also more typical for the symptomatic PHPT ($P<0.001$). Cardiovascular disease was recorded in 48% of patients, more frequent in the symptomatic group ($P<0.001$). 811 patients (14%) had a suspicion for hereditary PHPT, however a genetic analysis was conducted in 183 cases revealing the mutations in *MEN1, CDC73, RET* genes in 107, 6 and 2 cases, respectively. As expected, the PHPT manifestation in MEN-1 group was earlier 33 [26; 48] compared to sporadic disease 59 [52; 66] years ($P<0.001$), average duration of disease before diagnosis was 0 [0; 4] vs 0 [0; 2] years ($P=0.055$). Surgical treatment has been performed in 3206 (53%) of patients with remission achievement in 87%, the relapse or persistence after surgery were recorded in 13%. Parathyroid carcinoma was verified in 101/2666 (4%) of cases, atypical adenoma in 53/2666 (2%), adenoma in 2227/2666 (84%), hyperplasia in 285/2666 (11%). Drug therapy was prescribed in 2889 (48%) of patients, with a predominance of cholecalciferol prescription.
Conclusion
The detection rate of PHPT has increased in recent years in the Russia, which is associated with start of online registration. However, the majority of patients remained symptomatic that indicates delayed diagnosis and requires further modifications of medical care.

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EP134

Variations in plasma free 25-hydroxyvitamin D concentrations during intermittent fasting are independently correlated with amino acid intake among meat and non-meat eaters

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Background
Data on the effects of different dietary patterns on free 25-hydroxyvitamin D [25(OH)D] and vitamin D binding protein (VDBP) concentrations are scarce. Our objective was to prospectively assess changes over time in these parameters and possible correlations with diet composition among overweight adults who followed a pescatarian Orthodox intermittent fasting (OF) regimen and controls who followed a low-fat 12:12 diet for 7 weeks.
Methods
Total and free 25(OH)D, parathyroid hormone, VDBP, and anthropometric data were evaluated in 59 Orthodox fasters and 46 controls at three time points: at baseline, 7 weeks after the implementation of diets, and 5 weeks after the participants returned to their typical eating habits (12 weeks from baseline). The intake of amino acids for both diets was evaluated at all time points and possible associations with longitudinal changes in markers of vitamin D homeostasis were explored.
Results
Free 25(OH)D concentrations increased in both groups during the study. At 7 weeks, Orthodox fasters had higher concentrations than controls (9.52 ± 4.97 vs 4.96 ± 2.08 ng/ml, $P=0.003$). In the OF group, VDBP concentrations increased at 7 weeks compared to baseline values (286.37 ± 86.90 vs 230.11 ± 58.46 μg/ml, $P=0.004$), followed by a decrease at 12 weeks compared to 7-week measurements (234.66 ± 57.82 vs 286.37 ± 86.90 μg/ml, $P=0.032$). In contrast, a decrease in VDBP concentrations of controls was observed at 7 weeks compared to baseline (206.94 ± 40.01 vs 277.70 ± 76.01 μg/ml, $P=0.008$), followed by an increase at 12 weeks compared to 7-week values (290.12 ± 76.28 vs 206.94 ± 40.01 μg/ml, $P=0.014$). An increase in amino acid intake between baseline and 12 weeks was independently correlated with higher free 25(OH)D values at 12 weeks for both groups.
Conclusion
Our findings suggest that diet composition can affect free 25(OH)D concentrations, through variations in amino acid intake, independently of exposure to sunlight, and provide novel mechanistic insights into the future planning of vitamin D supplementation strategies and food fortification policies.

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EP135

Acquired Parathyroid Hormone Resistance–a Possible Disease

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Introduction
Acquired PTH Resistance (Acquired Pseudohypoparathyroidism) appears to be an extremely rare disease.
Case Report
A 19-year old man with history of brain medulloblastoma treated by surgery, radiotherapy and chemotherapy 9 years earlier was admitted to hospital in 2019 due to new-onset hypocalcemia. Patient presented with muscle cramps in legs, a tingling sensation in hands and feet, numbness around the mouth, and memory disturbances. Previously serum calcium levels were normal. Until the age of 10, psychophysical development was normal. Family history of calcium or PTH abnormalities was negative. Physical examination revealed positive Trousseau's sign, alopecia, lower limbs paresis, and mental retardation most likely due to the brain cancer. The biochemical evaluation showed low level serum calcium and ionized calcium as follows: 7.9 mg/dl and 0.98 mmol/l, high level phosphorous: 6.8 mg/dl, high level PTH: 780 pg/ml, normal level 25OHD3: 70 ng/ml, low level calcium diurnal urine collection: 41 mg/24 h.There were no other endocrinopathies nor renal and liver failure. Ultrasound examination showed no evidence of nephrolithiasis or nephrocalcinosis and x-ray scans revealed no signs of osteodystrophy. There were no cerebral calcifications. Treatment with calcium carbonate and alphacalcidol was initiated. The symptoms of tetany equivalents subsided and the level of calcium stabilized. PTH levels remained high despite calcium and magnesium normalization. The PTH resistance, probably acquired, was recognized. In the 4-year follow-up, the course of the disease was improved and the doses of vitamin D and calcium carbonate were significantly reduced.
Discussion
Genetic causes of PTH resistance become apparent in early childhood. At discharge, we suggested an acquired form of PTH receptor resistance, perhaps antibody or mutation related. We have no scientific methods to confirm this. Spontaneous improvement of the clinical course and alleviation of disorders in the last 4 years, may also speak in favor of an immunological mechanism. Uremic patients may develop antibodies against the PTH receptor[1]. Since the report in NEJM in 2021, we know that an acquired variant of the pseudohypoparathyroidism is possible[2]. The mechanism of the disease in the described patient is unknown, however, drug immunization cannot be ruled out despite the use of old-generation cytotoxic drugs. Tyrosine kinase and immune checkpoint inhibitors were not used. Therefore, further research is needed.
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EP136

Infection with the human immunodeficiency virus is characterized by a downregulation of the inverse relationship between irisin and parathyroid hormone independently of vitamin D status

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Background
Infection with the human immunodeficiency virus (HIV) predisposes to endocrine disorders, manifesting as a metabolic phenotype that affects the entire adipose-musculoskeletal unit (AMS). The present cross-sectional study aimed to investigate differences in irisin and adiponectin concentrations between people living with HIV and healthy controls, as well as to explore potential correlations between the levels of the aforementioned adipokines and markers of calcium homeostasis.
Methods
46 HIV-infected individuals (all men), with a mean age of 52.85 ± 8.48 years and a body mass index (BMI) of 25.76 ± 2.65 kg/m^2 and 39 healthy controls (all men) with a mean age of 45.44 ± 9.17 years and a BMI of 28.44 ± 6.29 kg/m^2 were included in the study. Anthropometric data, adipokine levels, 25-hydroxyvitamin D [(25(OH)D)] status and parathyroid hormone (PTH) concentrations were evaluated in the two groups. The Mann Whitney U test was used to assess differences between the HIV group and the control group. Pearson's correlations and partial correlations for the relationship between adiponectin, irisin, and PTH levels were examined. The results were adjusted for several confounders, including 25(OH)D levels, body fat, muscle mass, and mean exposure to ultraviolet B radiation during the previous 45 days before blood sample collection.
Results
The HIV group had a lower body fat mass (20.76 ± 6.18 vs 33.55 ± 7.60 kg, $P <$ 0.001) and a higher muscle mass (59.09 ± 8.13 vs 50.71 vs 12.08 kg, $P = 0.009$) compared to the control group. Mean adiponectin concentrations were significantly lower in the HIV group compared to the control group: 5868 ± 3668 vs 9068 ± 4277 ng/ml, $P = 0.011$. The same was applicable to irisin concentrations: 8.31 ± 8.17 (HIV) vs 29.27 ± 27.23 (controls) ng/ml, $P = 0.013$. A statistically significant and negative correlation was observed between irisin and PTH in the control group (r=-0.591; $P = 0.033$). In contrast, no significant correlation was observed between PTH and irisin in the HIV group ($P = 0.898$).
Conclusion
Our results suggest a possible down-regulation of the inverse relationship between PTH and irisin in HIV patients and highlight that AMS dyshomeostasis could be involved in the development of skeletal and adipose HIV-related morbidities.

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EP137

Histomorphometric parameters of parathyroid glands after 60 days of sodium benzoate administration

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Sodium benzoate (the food additive E211) is widely used as a preservative in the food and pharmaceutical industries. A direct correlation between sodium benzoate intake and the development of sensibilization, nephrotoxicity and hepatotoxicity, disorders of puberty, and genotoxicity has been established. However, the literature does not provide data on changes in morphometric parameters of parathyroid glands after long-term use of sodium benzoate. The aim of this work is to study the effect of 60-day sodium benzoate administration on the histomorphometric parameters of the parathyroid gland in rats. The experiment was performed on 18 white male mature rats divided into three groups. In group 1, animals were injected daily with 1 ml of sodium chloride through a feeding tube for 60 days, in groups 2 and 3, rats were injected with 1 ml of sodium benzoate solution at a dose of 500 mg/kg and 1000 mg/kg, respectively. Histological samples were prepared according to the standard procedure, sections were stained with hematoxylin-eosin and subjected to morphometry. Statistical analysis of the numerical data was performed using the Statistika 5.1 license program. In group 2, we observed a decrease by 1.47% ($P > 0.05$) in the largest size of parathyroid gland in comparison with group 1. The smallest size of the parathyroid gland decreased by 0.84% ($P > 0.05$), the number of nuclei of chief cells per unit section area decreased by 3.58% ($P > 0.05$), the mean diameter of chief cell nuclei decreased by 5.12% ($P < 0.05$), and functional index (number of nuclei of chief cells per unit section area*mean diameter of chief cell nuclei/20) decreased by 5.17% ($P < 0.05$). In group 3, changes in morphometric parameters of the parathyroid gland became more intense. The largest size of parathyroid gland decreased by 2.45% ($P > 0.05$), the smallest size of the parathyroid gland decreased by 2.65% ($p > 0.05$), the number of nuclei of chief cells per unit section area decreased by 5.27% ($P < 0.05$), the mean diameter of chief cell nuclei decreased by 10.12% ($P < 0.05$), and the functional index decreased by 8.11% ($P < 0.05$). 60-day intake of sodium benzoate causes dose-dependent changes in the histomorphometric parameters of the parathyroid glands in rats, which are indicative of their hypofunction.

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EP138

Clinical characteristics of sporadic and MEN1-associated primary hyperparathyroidism in young patients

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Introduction
Primary hyperparathyroidism (PHPT) is commonly the most early manifestation of multiple endocrine neoplasia syndrome type 1 (MEN1), but it can also occur in young patients without any inherited disorders. The aim of our study was to compare the clinical characteristics of PHPT in young patients with MEN1 syndrome and with sporadic disease.
Patients and Methods
The study included 72 patients with MEN-1 associated PHPT and 168 patients with sporadic disease. All patients were tested for MEN1 mutations. Electronic medical records were used to analyze clinical data of each patient. Patients who had sufficient data at the time of manifestation of PHPT (before the first surgery) were included.
Results
Both groups consisted mostly of young patients and there was no significant difference in the age of manifestation: 31 [25; 39] in the MEN1-group vs 34 [29; 37] in sporadic PHPT ($P = 0.308$). We did not receive a difference in preoperational levels of parathormone (145.2 pg/ml [98.7; 227.0] in MEN1 group and 152.07 pg/ml [113.90; 241.38] in sporadic PHPT, $P = 0.248$, as well as in albumin-corrected total blood calcium, phosphorus, and daily calciuria ($p > 0.05$ for all)). Also, no statistical difference was found in postoperative levels of PTH ($P = 0.605$) and total blood calcium ($P = 0.466$). Our groups did not differ in the prevalence of nephrocalcinosis/nephrolithiasis (59% in the MEN1group and 63% in the sporadic PHPT, $P =$ 0.615). Bone mineral density less than -2.0 SD (Z-score) was found more often in MEN1group: 54 vs 34% in sporadic patients, $P = 0.031$. There were significant differences in the preoperative number of the parathyroid (PT) tumors at the time of the primary surgery (95% of patients with sporadic PHPT and 41% of patients in the MEN1 group had only one PT tumor preoperatively, $P < 0.001$). Differences were also obtained by histological characteristics of the PT tumors (the frequency of adenoma, hyperplasia, and carcinoma occurrence ($P < 0.001$)), recurrence of PTHT after the surgery (36% of patients in MEN1 group and 1% in sporadic PHPT, $P <$ 0.001), and family history of other endocrine neoplasia (69% of patients in MEN1 group and 18% in the sporadic PHPT, $P < 0.001$).
Conclusion
Number of PT tumors, their histological characteristics, recurrence rate and family history should be taken into consideration when evaluating young patients with PHPT.

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EP139

Differential diagnosis between classic primary-, normocalcemic- and secondary hyperparathyroidism based on PFI and WI

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Introduction
Patients with primary hyperparathyroidism (PHPT) present high calcium and PTH levels while some patients present also high PTH levels but normal calcium levels (NHPT) and such patients be considered as having normocalcemic hyperparathyroidism. On the other hand vitamin D deficient patients develop secondary hyperparathyroidism (SHPT). Sometimes normocalcemic- and secondary hyperparathyroidism coexist. Therefore in clinical settings it is very difficult to distinguish primary hyperparathyroidism and normocalcemic hyperparathyroidism from secondary hyperparathyroidism.
Aim
The aim of our case control study is to differentiate these entities using the parathyroid functional index (PFI = PTH × Ca devided by P) and the Wisconsin Index (WI = PTH × Ca).

Patients and Methods
Twenty seven patients with PHP, 15 patients with NPHPT, 38 patients with SHPT and 47 apparently healthy (NC) were included. All patients had normal renal function. In all participants serum calcium, phosphorus, PTH and albumin were measured and corrected calcium, PFI and WI were evaluated.
Results
The PHPT group had the highest PFI compared to NHPT group ($P=0.02$) and also to the other two groups (SHPT and NC, all $P<0.0001$). The WI was higher in the PHPT group compared to SHPT group ($P<0.0001$) and to NC group ($P<0.0001$). WI was also higher in the NPHPT group compared to NC group ($P<0.0001$). In the healthy individuals (NC group) the highest values of PFI (18.41) and of WI (20.81) were taken as cut-off values and based on this sensitivity and specificity of the two indexes were evaluated and are presented in the following table.
Conclusion
PFI and WI can be useful in the differential diagnosis of hyperparathyroidism. It seems that the PFI performs slightly better than the WI in distinguishing patients with PHPT and NHPT from healthy individuals, whereas the WI distinguishes only patients with PHPT from healthy individuals.

	PHPT	NHPT	SHPT
PFI Sensitivity (%)	100	100	100
Specificity (%)	100	100	63.2
WI Sensitivity (%)	100	97.9	97.9
Specificity (%)	100	93.3	73.7

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EP140

Patient with Ia pseudohypoparathyroidism and the novel mutation in the GNAS gene

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Introduction
Pseudohypoparathyroidism (PHP) is an orphan disease caused by a mutation in the *GNAS* gene encoding the α-subunit of G-protein. PHP is characterized by multihormonal resistance. A correlation between the genotype and phenotype of patients with *GNAS* mutations hasn't yet been described.
Clinical Case
Patient T., 19 years old male, admitted to our Centre with general weakness and overweight. Hypocalcemia, hyperphosphatemia, increased serum PTH, TSH and psychomotor retardation were first detected at the age of 8 months, however, the diagnosis was clinically made at age of 2 years. The patient's elder brother died at the age of 4 years for unknown reason (symptoms consistent with PHP), the mother, elder sister and her 2 daughters were healthy. From 2003 to 2008, the patient received alfacalcidol 1.2 mg daily without normocalcemia achievement. Further alfacalcidol was replaced with cholecalciferol 25,000 IU daily. At the same time, levothyroxine was prescribed. At the age of 4 years, the patient was diagnosed with diabetes insipidus followed by desmopressin therapy. At admission, T.'s consciousness was clear, however, he was partially oriented in space and time. T. had II stage obesity (BMI - 36.73 kg/m^2). There were a posture disturbance, shortening of the metatarsal bones of 1,2,4,5 fingers of both hands, shortening and deformation of 4 toes (phenotype of Albright hereditary osteodystrophy). Laboratory tests revealed normocalcemia - 2.16 mmol/l (2.15-2.55), normophosphatemia - 1.33 mmol/l (0.74-1.52), normocalciuria - 3.7 mmol/d (2.5-8), increased serum PTH -102.4 pg/ml (15-65). 25(OH) vitamin D was above 150 ng/ml. We temporarily discontinued cholecalciferol and prescribed alfacalcidol 0.75 mg daily with achievement of normocalcemia, normophosphatemia. Brain MRI visualized symmetrical zones of calcification in the subcortical nuclei and nuclei dentati of cerebellum. Nephrocalcinosis/nephrolithiasis were excluded. Given the lack of evidence for the diabetes insipidus a trial withdrawal of desmopressin was carried out, and the plasma and urine osmolality, blood serum electrolytes remained within the laboratory reference range. The typical MRI signal of the neurohypophysis was preserved. *GNAS* gene sequencing showed a novel heterozygous mutation, whose pathogenicity was proved.
Conclusion
PHP is caused by complex genetic and epigenetic defects. As a result, the path to diagnosis can be long and difficult. Determining the pathogenicity of novel GNAS mutations will improve understanding of gene function and expected clinical manifestations.

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EP141

Risk factors of hypoparathyroidism after total thyroidectomy: A prospective study

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Objective
Identify the risk factors of hypoparathyroidism (hypoPT) after Total thyroidectomy (TT).
Patients and Methods
Our study is a randomised clinical trial. It enrolled patients who underwent total thyroidectomy at the department of ENT surgery at Habib Bourguiba Hospital in Sfax between November 2020 and august 2021. We studied age, gender, type of surgery, duration of surgery, vitamin D level, magnesium level, histopathological exam, inadvertent resection of parathyroid gland, central neck dissection (CND) and the impact of prophylactic supplementation with oral calcium and vitamin D.
Results
Forty-seven patients were recruited for this study. They were divided into two groups: group 1: with prophylactic supplementation (24 patients) and group 2: without prophylactic supplementation (23 patients). We studied the impact of the risk factors on day one parathormone level. There were 19 patients with transient postoperative hypoparathyroidism. There was not a significant difference between the two groups regarding Day 1 PTH level. The results of univariate analysis showed a significant relation between transient hypoPT with severe hypovitaminosis D ($P=0.001$), operative time($P=0.01$), CND ($P=0.03$) and accidental resection of parathyroid gland ($P=0.04$). Multivariate analysis did not show any relation of hypoPT with any risk factor. The prophylactic supplementation allowed to significantly reduce the occurrence of biological and clinical hypocalcaemia.
Conclusion
In multivariate logistic regression we did not identify any independent risk factor. This explains the difficulty to predict the occurrence of such a complication. For that, prophylactic postoperative supplementation with oral calcium and vitamin D seems to be a safe choice to prevent postoperative hypocalcaemia.

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EP142

Chronic hypoparathyroidism: Predictors of complications according to the Russian Registry

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Background
Chronic hypoparathyroidism is a relatively rare disease associated with various complications. The analysis of large databases of patients with chronic hypoparathyroidism is a necessary tool to enhance quality of medical care, as well as to determine the therapeutic approaches and prognostic markers of the disease.
Aims
To describe complications associated with chronic hypoparathyroidism and determine predictors of their development according to the Russian Registry.
Materials and Methods
The cross-sectional, observational, continuous study based on the Russian Registry of patients with hypoparathyroidism was carried out including 708 patients from 64 regions of the Russia. ROC-analysis was used to find cut-off points of predictors positively associated with complications.
Results
Nephrolithiasis was confirmed in 34.6%, nephrocalcinosis - in 11.7% of cases, 24.9% of patients met the criteria of CKD 3a-5 stages (glomerular filtration rate (GFR)-EPI less than 60 ml/min/1.73 m^2). The predictors of renal complication were non-target 24 h urinary calcium level ($P=0.033$, U-test, Benjamini-Hochberg correction $P_0=0.004$) and upper-reference range serum calcium level ($P<0.001$, U-test, $P_0=0.05$). Patients with preserved renal function took significantly lower doses of alfacalcidol - 1.00 μg/day [0.75; 2.00] vs 1.50 μg/day [1.00; 2.00] compared with patients with an GFR less than 60 ml/min/1.73 m^2 ($P=0.033$, U-test, $P_0=0.025$). Differences in doses of calcium carbonate weren't obtained ($P=0.270$, U-test). ROC-analysis revealed cut-off points of serum calcium level associated with the risk of GFR less than 60 ml/min/1.73 m^2: 1.97 for albumin-adjusted (AUC=0.651), 2.12 for total (AUC=0.610) and 1.08 for ionized (AUC=0.637) calcium levels. The cut-off point

for the decreasing GFR was duration of hypoparathyroidism–14.5 years, with a 3.58-fold increased risk. Also the excess of 24 h urinary calcium level more than 4.02 mmol/day was associated with an increased risk of structural disorders in the kidneys (AUC = 0.594). The cataract was confirmed in 47% patients, 82% of them had postsurgical hypoparathyroidism. The longer duration (10.5 years [6.0; 17.0] vs 6 [4.0; 9.0]) of hypoparathyroidism was associated with more frequent cataract ($P <$ 0.001, U-test, $P_0 = 0.004$) and this does not depend on medicaments and their doses. ROC-analysis showed cut-off points of serum ionized calcium level of 1.03 mmol/l, if it is not reached, the risk of developing cataracts increases (AUC = 0.652). The cut-off point for the development of cataracts was duration of hypoparathyroidism–10.5 years, with a 4.39-fold increased risk.

Conclusions

Hypoparathyroidism is associated with higher risks of renal stone formation, decreased GFR, cataract - especially in patients with longer duration of disease. The non-target serum calcium level was associated with renal and ophthalmological complications.

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EP143

Primary hyperparathyroidism in pregnancy: A case report

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Introduction

Despite its rarity, the most common cause of hypercalcemia in pregnancy is primary hyperparathyroidism (PHPT). This disorder increases the risk of miscarriages, premature birth, intrauterine growth restriction, severe pancreatitis, preeclampsia, and neonatal hypocalcaemic tetany if not diagnosed and properly managed.

Case

A 31-year-old woman with 13 weeks of pregnancy and acute pancreatitis was admitted to the Obstetrics department. Since the 6th week of pregnancy, she has suffered from intense nausea, vomiting, and great general weakness. To find the cause of acute pancreatitis, the calcium level was measured, and severe hypercalcemia albumin-corrected at 3.5 mmol/l was found. Hypophosphatemia 0.61 mmol/l, hypomagnesemia 0.36 mmol/l, hypokalemia 2.27 mmol/l, anemia Hb 89 g/l, parathyroid hormone (PTH) 32.37 pmol/l, vitamin D 74.5 nmol/l, normal renal function, and hypercalciuria in 24-h urine at 15.42 mmol/l are also found in the laboratory. Abdominal-pelvic ultrasound revealed no kidney calcification and confirmed no abnormalities in the fetus. A neck ultrasound revealed a $3.1 \times 1.1 \times 2.4$ cm hypoechogenic mass under the left thyroid lobe, which looked more like an enlarged lymph node than a parathyroid gland, so the mass was aspirated with a fine needle. From the start of the hospitalization and while waiting for the puncture results, a large amount of infusion therapy was administered, lowering the calcium level to 2.8 mmol/l. Other electrolyte imbalances were also corrected. Cytology results confirmed a parathyroid gland, and a parathyroidectomy was performed in the 15th week of pregnancy. After surgery, PTH was 0.61 mmol/l, and the lowest albumin-corrected calcium level was 2.2 mmol/l on the 4th day after surgery. Calcium, magnesium, and vitamin D supplements were administered to prevent the symptoms of hypocalcemia. The patient complained of mild numbness in her arms for two days following surgery. The calcium level normalizes rapidly after surgery, and the mother and fetus were both in good health when the patient was released from the hospital for follow-up care. Postoperative pathology suggested a parathyroid adenoma.

Conclusions

The diagnosis of PHPT in pregnancy is difficult due to the physiological changes in pregnancy that can mask the clinical symptoms of hypercalcemia. When pregnant women have intensive digestive disorders, fatigue, polyuria, and muscle weakness, calcium levels should be measured to rapidly establish appropriate treatment and reduce the risk of maternal and fetal complications. Surgery is the first choice of PHPT treatment and it is the safest during the second trimester of pregnancy.

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EP144

Differences in the clinical, laboratory, and operative variables between pre-menopausal and post-menopausal primary hyperparathyroid women: a single-center experience

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Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disorder wherein enlargement of one or more of the parathyroid glands causes autonomous overproduction of the parathyroid hormone (PTH), which leads to high serum calcium levels.

Objective

Comparison of clinical, laboratory, and operative variables between premenopausal (pre-M) and postmenopausal (post-M) women with PHPT.

Materials and Methods

A retrospective analysis of the data of female patients who underwent surgery for PHPT at a single centre, from January 2011 to December 2020, was done. Patients with familial PHPT and secondary hyperparathyroidism were not included.

Results

Of the 130 women with PHPT, 44.6% were pre-M and 55.4% were post-M. A significantly higher number of pre-M females were symptomatic compared to post-M females (pre-M vs post-M, 84.5% vs 68.1%, $P = 0.031$). Renal calculi were more common in pre-M women (34.5% vs 18.1%, $P = 0.032$), while rest of the clinical features of bone disease, gastrointestinal manifestations, proximal myopathy and neuropsychiatric manifestations were comparable between the two groups. Proportion of women with osteoporosis (6.7% vs 19.4%, $P = 0.071$), hypertension (13.8% vs 34.7%, $P = 0.012$) and diabetes mellitus (3.5% vs 16.7%, $P = 0.033$) was lesser in the pre-M group. Elevated serum alkaline phosphatase levels were significantly more prevalent in the pre-M group (37.9% vs 20.8%, $P = 0.032$). Mean serum calcium (12.35 ± 1.28 vs 11.96 ± 1.22 mg/dl, $P = 0.079$), median serum PTH (334 vs 239 pg/ml, $P = 0.051$), and median weight of the operated adenomas (1.75 vs 1.45 g, $P = 0.075$) were also higher in pre-M females. The proportion of ectopic adenomas and multiple adenomas, pre-surgery adenoma localization rates, and disease cure rates did not differ according to the menopausal status. Occurrence of post-surgery hungry bone syndrome was higher in the pre-M women (15.5% vs 1.4%, $P = 0.008$).

Conclusion

The majority of women with PHPT are post-M, but symptomatic presentation is more common in pre-M females. The severity of the disease, and occurence of hungry bone syndrome appears to be more in pre-M women, however, imaging and operative variables generally did not significantly differ between the two groups.

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EP145

Hypocalcaemia induced dilated cardiomyopathy

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Introduction

Dilated cardiomyopathy is the third most common reason for heart failure and transplantation worldwide. The etiology of dilated cardiomyopathy often remains unclear, but in certain cases we can discover the cause, which can then contribute to better and more causal treatment.

Observation

We present a case of a 47-year-old man without any significant comorbidities in his medical history. In 2015 he underwent two hemithyroidectomies with a neck lymph node dissection due to a multifocal papillary thyroid cancer. The second hemithyroidectomy was complicated by a left-sided recurrent nerve paresis and severe postoperative hypocalcaemia caused by the accidental parathyroid removal. The surgery was followed by a radioiodine ablation and levothyroxine suppressive treatment. The radioiodine had to be reapplied twice because of a persistent biochemical incomplete response. From the beginning it was very difficult to achieve adequate calcium substitution mainly because of a previously documented noncompliance of our patient. He was repeatedly intolerant to calcium and vitamin D supplements and therefore adjusted doses himself. In 2020 he was hospitalized due to signs of a heart failure and was diagnosed with dilated cardiomyopathy. Chronic hypocalcaemia and the uncompensated post-operative hypoparathyroidism were considered as the most probable cause. Patients heart failure progressed rapidly, which led to LVAD (left ventricular assist device) implantation as a bridge for heart transplantation. Therefore, restoring normocalcaemia became a priority. We started newly available rhPTH (1-84) therapy, that successfully normalized calcium levels. Concerning the thyroid cancer, the thyroglobulin is still rising and newly there is a paratracheal thyroid residuum visible on the PET/CT scan, which will require surgical intervention.

Therefore, the heart transplantation is being postponed. However, according to the latest echocardiography there is an improvement of ejection fraction (from less than 20% to 30-35%) with a partial reverse myocardial remodelling and reduction of the end-diastolic diameter of the left ventricle.
Conclusion
Hypocalcaemia induced dilated cardiomyopathy is a rare condition but previous case reports suggest its potential reversibility after a timely hypocalcaemia correction. In our case there is a slight improvement, however not enough to prevent him from the heart transplantation which is now being postponed due to the planned surgery of the thyroid residuum. The non-compliance has contributed significantly to the severity of his condition.

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EP146

The calcium-to-phosphorus ratio in the diagnosis of parathyroid disorders

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Introduction
The diagnosis of primary hyperparathyroidism and hypoparathyroidism is still challenging because of the increasing frequency of non-classical presentations. The calcium-to-phosphorus ratio (Ca/P) (CPR) is an inexpensive biochemical marker that could be useful to diagnose parathyroid disorders.
Aim
The aim of this study was to assess the performances of CPR in the diagnosis of primary hyperparathyroidism and hypoparathyroidism.
Methods
This was a single-center, cross-sectional study including 32 patients with PHPT, 32 patients with hypoparathyroidism, and 32 controls. Total serum calcium (mg/l), serum phosphorus (mg/l), and parathyroid hormone (PTH) (ng/l) levels were recorded for all the participants. The diagnostic performance of the CPR was evaluated using the receiver operating characteristic (ROC) curve to define cut-off points. Sensitivity and specificity were calculated.
Results
The mean CPR was 1.58 ± 0.39 in patients with hypoparathyroidism, 5.37 ± 1.28 in patients with primary hyperparathyroidism, and 2.94 ± 0.49 in controls ($P < 10\text{-}3$). It was positively correlated with the PTH level ($r = 0.618$, $p < 10\text{-}3$). However, CPR was not correlated with age, body weight, and body mass index. CPR had an area under the ROC curve of 0.977 (95%-confidence interval: 0.941-1) in the diagnosis of primary hyperparathyroidism with an optimum cut-off level of 3.70, providing a sensitivity of 94% and a specificity of 100%. The area under the ROC curve of CPR in the diagnosis of hypoparathyroidism was 0.987 (95%-confidence interval: 0.969-1). A CPR level below 1.99 was defined to identify patients with hypoparathyroidism with a sensitivity of 97% and a specificity of 91%.
Conclusion
Our results demonstrated the accuracy of CPR as a reliable tool for the diagnosis of both primary hyperparathyroidism and hypoparathyroidism.

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EP147

Long-term outcomes of parathyroidectomy in patients with primary hyperparathyroidism from patient's perspective

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Background
A parathyroidectomy (PTX) is the preferred standard treatment for patients with primary hyperparathyroidism (PHPT). the assessment of the surgery success from patient's perspective is important to provide patient-centered care.
Aim
We aimed to evaluate QoL changes in PHPT patients during 2-years follow-up after PTX and to identify preoperative predictors of meaningful QoL improvement after surgery.
Materials and Methods
The single-center observational prospective study was carried out from September 2019 to October 2022. All the patients underwent routine PTX. The objective success of surgery was confirmed by pathology confirmation of hyperfunctioning parathyroid tissue and postoperative normalization of Ca^{2+} and p-PTH. Patients filled out generic and specific QoL questionnaires–RAND SF-36 and PHPQoL before surgery, at 3, 12 and 24 months after PTX. To evaluate QoL changes after surgery GEE method with adjustment to gender, age, baseline QoL, clinical type of PHPT and level of hypercalcemia was applied. Binary logistic regression and χ^2 were used to explore the association between preoperative variables and whether the patient had experienced meaningful QoL improvement in ≥ 9 points by PHPQoL total score.
Results
A total of 72 PHPT patients (median age–53.1 ± 9.9 years, 94.4% females) who had objective surgery success were included in the analysis. From the total 70.8% patients had «symptomatic» PHPT, 29.2%–"asymptomatic" PHPT; mild hypercalcemia was detected in 65.3% patients, moderate or severe hypercalcemia–in 34.7% patients. During the entire follow-up period there was significant improvement in QoL after surgery by all scales of SF-36 questionnaire ($P < 0.01$), excluding bodily pain, and by the PHPQoL total score (GEE, $P < 0.001$) as compared with their preoperative values. Meaningful QoL improvement by PHPQoL total score (QoL response) was reported in 61.1% patients (QoL responders); the proportion of QoL responders was similar in patients with "symptomatic" and "asymptomatic" PHPT (60.8% vs 61.9%, $p > 0.05$). Among preoperative variables, including type of PHPT ("symptomatic" or "asymptomatic"), Ca^{2+}, p-PTH, disease duration, presence of comorbidities, patient's age and education along with QoL parameters, only mental component of QoL by PHPQoL was significantly predicting of QoL response after surgery (OR = 0.927, 95%CI = 0.874-0.984, $P = 0.013$).
Conclusions
Successful PTX was accompanied with remarkable QoL improvement for at least 24 months after surgery in both "symptomatic" and "asymptomatic" PHPT patients. Mental QoL component was the only one factor significantly predicting QoL response after surgery. This finding suggests that patients without overt clinical manifestation or prominent hypercalcemia, but with derangement of mental health may benefit from PTX.

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EP148

Efficacy and safety of Cinacalcet therapy for patients with primary hyperparathyroidism: A retrospective observational study

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Introduction
Cinacalcet therapy remains the only alternative to elective parathyroidectomy (EP) for lowering serum calcium (Ca) in patients with primary hyperparathyroidism (PHPT). National Institute of health and Care Excellence (NICE), UK support use of cinacalcet in symptomatic patients with PHPT who decline surgery (or deemed unfit for surgery), if serum Ca levels > 2.85 mmol/l. The limitation in wider use of cinacalcet remains cost effectiveness apart from limited data related to its long term efficacy and safety.
Objective
To evaluate long term safety & efficacy of cinacalcet in patients with PHPT.
Methodology
We carried out a retrospective observational study of all patients with a biochemically confirmed diagnosis of PHPT who were initiated on cinacalcet therapy in Cwm Taf healthboard. The clinical records were accessed and with a focus on noting the indication, duration, dose and side effects of cinacalcet. Biochemical results were analysed for Serum Ca, Phosphate, PTH (pre and post cinacalcet therapy) and a note was made of relevant radiological investigations.
Results
We identified a total of 56 patients with PHPT who received cinacalcet therapy from September 2013 to January 2021. Cinacalcet use was observed to be associated with a reduction of mean serum calcium level by 0.4 mmol/l ($P < 0.001$; CI 0.369- 0.484). There was a decrease in mean serum PTH level by 3.6 mmol/l ($P < 0.001$; -1.6914 to -5.438; $n = 17$). The adverse drug reactions (ADR) encountered in this study were mainly gastrointestinal (GI) symptoms such as nausea, vomiting and abdominal discomfort. 5 of the patients discontinued cinacalcet due to GI side effects. Mild hypocalcaemia was noticed in 2 of the patients.
Discussion
Our retrospective observational study results show a significant as well as sustained reduction in serum Calcium and PTH levels with use of cinacalcet in patients with PHPT. This therapy is generally well tolerated with no long term safety concerns. The threshold for offering cinacalcet therapy should be lowered in patients with PHPT considering significant reduction in serum calcium and PTH levels which may translate into improved intermediate to long term secondary outcomes.

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EP149

The daily calcium profile in patients with chronic hypoparathyroidism depending on different 25(OH) vitamin D level

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Introduction
Chronic hypoparathyroidism is a rare disease, which usually treated with active forms of vitamin D and oral calcium. Supplementation with native vitamin D can be useful both for achieving "non-skeletal" effects of vitamin D and for a more stable serum calcium profile.
Aim
The aim of this study was to estimate the daily serum calcium and 24-hour urine calcium levels in patients with chronic hypoparathyroidism depending on different 25(OH) vitamin D (25(OH)D) values.
Methods
40 patients with chronic hypoparathyroidism (38 with postsurgical and 2 with idiopathic) were involved in the study. All patients were divided in two groups, matched on sex and age, according to the median level of 25(OH)D in the total group (1–with 25(OH)D <35.0 ng/ml; 2 - with 25(OH)D ≥ 35.0 ng/ml). To assess the variability of calcium during the day, the measurement of the total calcium (Ca_{total}) was carried out every 2 hours within 24 hours, albumin - once in the early morning (to calculate albumin-adjusted calcium, Caadj). All patients received conventional treatment with active metabolites/analogues of vitamin D (alfacalcidol, calcitriol) and calcium supplements.
Results
Serum 25(OH)D level was significantly higher in group 2 (28.45 ng/ml vs 44.15 ng/ml, $P<0.001$, U-test). There were no significant differences between groups by Ca_{total}, Ca_{adj} levels and daily calciuria. Patients with serum 25(OH)D level $\geq$ 35.0 ng/ml had significant tendency to achieve more often the target levels of Ca_{total} (128 vs 149 measurements during the day, $P=0.049$, χ^2). However, this tendency disappeared for Ca_{adj} ($P=0.517$, χ^2). The frequency of hypercalcemia by Ca_{adj} was significantly lower in patients with 25(OH)D ≥ 35.0 ng/ml ($P=0.006$, χ^2), but not for Ca_{total} (a trend, $P=0.042$, χ^2). As regards hypocalcemia, there were no significant differences by Ca_{adj} ($P=0.581$, χ^2) and it tends to lower frequency by Ca_{total} ($P=0.023$, χ^2).
Conclusion
The additional administration of native vitamin D in patients with chronic hypoparathyroidism may have some advantages, related to the general concept of worldwide vitamin D deficiency and better disease control. In this study, we did not confirm statistically significant differences for chronic hypoparathyroidism in the calcium profile depending on different 25(OH)D levels. But we obtained some promising statistical further studies are required.

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EP150

Low 25(OH) vitamin D levels are associated with Long COVID syndrome in COVID-19 survivors

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Low vitamin D levels were consistently reported as a risk factor for worse outcomes in hospitalized COVID-19 patients. Emerging evidences suggest that in 50–70% of COVID-19 survivors several post-COVID symptoms can be observed up to 3 months after acute-disease, representing a novel clinical condition defined Long-COVID syndrome. To date, the predisposing factors for this syndrome are still poorly understood. We retrospectively aimed at evaluating the influence of 25(OH) vitamin D levels on Long-COVID occurrence in patients previously hospitalized for COVID-19, re-assessed 6-months after discharge. Long-COVID was defined based on the National Institute for Health and Care Excellence-guidelines and approximately 500 patients were re-evaluated after the first pandemic-wave. While excluding patients with therapies/comorbidities affecting bone metabolism, and/or those admitted in ICU during hospitalization, only 50 Long-COVID patients were eligible for enrolment and compared in an age, sex, comorbidities and acute-disease characteristics-matched 1:1 ratio with non-Long-COVID patients. 25(OH) vitamin D was measured at hospital-admission and after 6-months. Median 25(OH) vitamin D levels were 14.7 and 20.6 ng/ml, at hospital-admission and at 6-month follow-up, respectively. At admission, vitamin D deficiency (25(OH) vitamin D <20 ng/ml) was found in 71 patients, and, at 6-month follow-up, in 46 patients. We observed lower 25(OH) vitamin D levels, evaluated at follow-up visit, in Long-COVID group than those without (20.1 vs 23.2 ng/ml, $P=0.03$). No statistically significant differences were observed regarding prevalence of vitamin D deficiency between those with and without Long-COVID. Regarding the different affected health areas evaluated in the entire cohort, we observed lower 25(OH) vitamin D levels in those with neurocognitive symptoms at 6-month visit (n.7) as compared to those without (n.93) (14.6 vs 20.6 ng/ml, $P=0.042$). In patients presenting vitamin D deficiency both at admission and at follow-up (n.42), those affected by Long-COVID (n.22) were characterized by lower 25(OH) vitamin D levels, evaluated at follow-up, compared to those not affected (n.20) (12.7 vs 15.2 ng/ml, $P=0.041$). In multiple regression analyses, lower 25(OH) vitamin D levels, evaluated at follow-up, resulted as the only variable significantly associated with the Long-COVID occurrence ($P=0.016$, OR 1.08-CI 1.01-1.15). In conclusion, COVID-19 survivors with Long-COVID have lower 25(OH) vitamin D levels as compared to matched patients without Long-COVID. Moreover, lower vitamin D resulted as an independent risk factor for the occurrence of this syndrome. Our data suggest that evaluating vitamin D levels in COVID-19 patients after hospital discharge and improving their vitamin D status when needed may be helpful in reducing the burden of COVID-19 sequelae.

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EP151

Evaluation of the efficacy and safety of long-term Cinacalcet in primary hyperparathyroidism

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Introduction
Cinacalcet is a positive allosteric modulator of the calcium sensing receptor successfully used to decrease serum calcium in primary hyperparathyroidism (pHPT) patients in the short-term, but long-term data are scarce. In this single-centre retrospective analysis, we investigated the efficacy and safety of cinacalcet in pHPT patients who received more than 5 years of treatment.
Methods
Statistical analysis was performed using free online software (www.socscistatistics.com) and Excel database statistics functions; a non-paired t-test was used in the analysis of pre-treatment biochemistry in low vs high dose cinacalcet therapy, and a paired t-test was used for the analysis of pre- vs post-treatment biochemistry. A P-value of <0.05 was considered statistically significant.
Results
21 patients (81% females) were treated for a mean of 7.3 years (SD 1.74). Patients were commenced on cinacalcet due to increased surgical and/or anaesthetic risk (8), persistent/recurrent disease (4) and patient unwilling to undergo surgery (3). 6 patients received cinacalcet since adenomas were not localized preoperatively. Initial dose was 30 mg/day in 76% of cases, with the remainder starting at 60 mg/day. Baseline calcium levels did not differ between the two different starting dose groups (11.35 mg/dl vs 11.84 mg/dl: P 0.06). 47% remained on same dose and 42% increased dose during follow up. Serum calcium level decreased significantly at 3 months (11.47 mg/dl vs 10.7 mg/dl; $P<0.05$), with 66% reaching serum calcium <10.5 mg/dl. Compared to basal levels, at last appointment calcium decreased significantly (11.47 mg/dl vs 9.7 mg/dl; $P<0.05$), phosphorus increased significantly (2.57 mg/dl vs 3.2 mg/dl; $P<0.05$). There was a non-significant decrease in PTH (217 pg/ml vs 191 pg/ml; $P=0.1$). 3 patient developed adverse events (myalgia, headache and no-specified), all of which could be managed without a definitive withdraw of treatment (temporal stop 2, decrease dose 1). 6 patients died during follow up, 5 of them were initially classified as "increased surgical and/or anaesthetic risk". One death could be related to HPP: pancreatitis, with calcium levels of 12.5 mg/dl probably due to temporal suspension of the treatment of unknown reason, with previous excellent calcium control. The rest of exitus were due to age related diseases. 2 patient developed hip fracture during treatment with cinacalcet.
Conclusion
Cinacalcet seems effective in lowering serum calcium and PHPT patients in the long-term. The high mortality of our study seems to be related to the fact that cinacalcet is mainly used in patients who are poor surgical candidate.

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EP152

Incidental hypercalcemia during denosumab treatment for osteoporosis: rebound phenomenon or occult primary hyperparathyroidism

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Introduction
Denosumab is an important treatment option for osteoporosis. Rebound hypercalcemia on discontinuation of denosumab is well documented. Denosumab can increase PTH, peaking within 2-4 weeks of administration and subsiding thereafter, therefore making diagnosis of primary hyperparathyroidism (pHPT) difficult.The aim of our case series is to review the calcium fluctuations in relationship to timing of denosumab administration and identify the possibility of rebound hypercalcemia during denosumab treatment.
Methods
A retrospective case-series analysis of patients discussed at metabolic bone multidisciplinary meeting due to elevated calcium on denosumab treatment (2019-2022) was conducted. Calcium was checked as part of standard care during denosumab treatment, and if elevated led to subsequent PTH measurement. Based on the timing of calcium measurement to denosumab administration, the hypercalcemia was classified as *pre-denosumab* (taken preceding denosumab administration), *post-denosumab* (within 3 weeks of administration of denosumab) or *mid-denosumab* (typically between 3 weeks post administration and 2 weeks before next injection)
Results
$n=16$; all patients had normal calcium preceding denosumab initiation. The patterns identified were:

A. *One-off pre-denosumab hypercalcemia*: ($n=3$): Elevated calcium noted only once; all were on a pre-denosumab sample. 2 of these had a high PTH on post-denosumab both of which normalized on subsequent pre-denosumab sample; one had persistent PTH throughout.
B. *Persistent pre-denosumab hypercalcemia*: ($n=2$). These patients had elevated calcium on more than one occasion on pre-denosumab samples. One patient had elevated PTH, but on post-denosumab sample.
C. *Likely pHPT*: ($n=5$): These patients had high calcium not only in pre but also in the post denosumab samples. 4 had elevated PTH.
D. *Inconclusive*: ($n=6$). These patients had documented hypercalcemia in pre and mid-denosumab samples but normal readings post-denosumab, therefore likely pointing towards calcium lowering effect of denosumab. 4 had documented high PTH.

Conclusion
Incidental hypercalcemia can be commonly encountered during denosumab treatment. A significant proportion of these patients may represent 'rebound' hypercalcemia and less likely to be true pHPT (groups A,B). The normal calcium readings preceding denosumab initiation, timing of the elevated reading (pre-denosumab being elevated) and a lack of consistent PTH raise (normal PTH despite being on Denosumab) may support the likelihood of this phenomenon during denosumab treatment. The possibility of pHPT being unmasked or incidentally idenfied needs to be considered too (groups C,D). This case series depicts the complexities and uncertainties of identifying an aetiology for high calcium during denosumab treatment and hence the need for multi-disciplinary approach and long term prospective studies.

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EP153

Phosphocalcium profile and prevalence of osteoporosis in patients with cushing's disease at diagnosis

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Introduction
Cushing's disease represents the most frequent etiology of endogenous cushing's syndrome. It is a severe condition associated to many comorbidities and increased mortality that occurs a long-term management to optimize these patients outcomes. This study aims to describe the phosphocalcium profile and to assess the prevalence of osteporosis in patients with cushing's disease.
Materiels and Methods
Retrospective and descriptive study, including 17 patients with cushing's disease hospitalized in the Endocrinology-Diabetology-Nutrition department of university hospital center Mohammed VI of Oujda between 2016 and 2022, we had excluded the cases where a bone densitometry was missing. Statistical analysis was performed by SPSS version 21 software.
Results
The average age was 34.8 ± 10.8 years, with a clear female predominance (70.6%). The average time to consultation after onset of symptomatology in our patients was 3.2 ± 3 years. The mean level of phosphorus in our series was 32.3 ± 4.5 mg/l, 5.8% of our patients had hypophosphatemia. On the other hand, none of our patients had hypocalcemia with a mean value of calcemia at 93.8 ± 3.1 mg/l. The mean vitamin D level in our series was 16.2 ± 7.9 ng/ml, hypovitaminosis D was described in 94.1% of the patients, of which 31.2% had vitamin D deficiency, while 62.9% were vitamin D deficient. Eighteen percent of our patients had osteoporosis, with a predominance of the lumbar spine in all patients. Osteopenia was found in 53% of the patients in our series, with involvement of the lumbar spine in all cases, 30% of whom had involvement of the lumbar spine associated with the femoral neck.
Discussion-Conclusion
Cushing's disease leads to many complications that heavily impact on life's quality and survival of affected patients. Cushing osteopathy is one of the most severe ones, in fact, the risk of fracture increases immediately with the onset of the disease, hence the need for rapid management in order to limit these complications and optimize the survival of these patients.
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EP154

Bone mineral metabolism in young hemodialyzed women with prolonged amenorrhea

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Introduction
Since chronic renal failure is accompanied with bone abnormalities, the term renal osteodystrophy has become widely accepted. In women, chronic renal failure is commonly accompanied by endocrine problems that cause irregular menstruation. The majority of investigations on renal osteodystrophy, however, have not considered the potential impact of these hormonal imbalances on the etiology of the bone changes observed in these patients.
Objective
In the current study, the bone mineral metabolism in a group of young hemodialyzed women with persistent amenorrhea was assessed and contrasted with women of comparable age and menstrual cycle
Method
The study included 70 women, of which 30 had persistent amenorrhea, which is the lack of menstrual blood for more than five months, and 40 had regular menstrual cycles. All patients underwent a bone mineral density (BMD) analysis that simultaneously assessed various biochemical parameters, intact parathyroid hormone (iPTH), sexual hormone measurements including total estradiol, follicle-stimulating (FSH), and luteinizing hormone, and markers of bone resorption such as the procollagen type 1 cross-linked carboxy-terminal telopeptide (ICTP). Unpaired observations were compared using the Student's t-test between two groups of data (two-tailed). The linear regression technique was used to compare two variables. P values below 0.04 were regarded as significant.
Result
Both groups had comparable levels of serum iPTH, calcium, and phosphorus. Amenorrheic women had greater serum levels of alkaline phosphatase. Despite being normal when compared to non-uremic women, the total serum estradiol levels in amenorrheic women was substantially lower than that of women who regularly menstruate. The amenorrheic women had considerably greater serum levels of FSH and ICTP. Compared to dialysis patients who had regular periods, the trabecular BMD in the lumbar spine was likewise considerably lower in amenorrheic women. Significant correlation was seen in the amenorrheic group between lumbar spine BMD and total estradiol levels.

Conclusion
These results demonstrated that when compared to regular menstruation women on dialysis, persistently amenorrheic young women on dialysis have reduced trabecular BMD and signs of accelerated bone resorption. It is yet to be determined how these findings may affect the course of uremic osteodystrophy in its natural state.

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EP155

A case with late-onset Ornithine Transcarbamylase Deficiency as a possible cause of osteoporosis

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Introduction
Ornithine transcarbamylase deficiency (OTCD) is a urea cycle disorder that causes the accumulation of ammonia, which can lead to neurocognitive problems in patients[1]. Here we report a 21-year-old man who was diagnosed with OTCD during investigation for secondary osteoporosis.
Case
The patient applied to the Endocrinology department complaining of widespread muscle-joint pain, shortening in height, nausea/vomiting attacks followed by protein-rich nutrition and weight loss (8 kilograms in 5 months). His personal history was otherwise unremarkable. He had a brother with osteoporosis diagnosed of 17 while being investigated for avascular necrosis of the hip. Bone mineral density measured with dual X ray absorptiometry showed a lumbar Z score-3.4 and a femur neck Z score of -2.2 concluded. Scoliosis was observed on X ray and no fracture is detected computed tomography. No hypogonadism was detected in laboratory tests performed for secondary osteoporosis. 1 mg dexamethasone suppression test was normal. Celiac markers, ANA and the enzymatic test for Gaucher's disease were negative. Serum calcium, phosphorus, magnesium and alkaline phosphatase, 24-hour urinary calcium, parathormone, and 25OH vit-D values and anterior pituitary hormones, were found to be within the normal limits as well as abdominal ultrasonography. The patient had suffered learning difficulties since childhood, protein intolerance and the development of nausea and vomiting attacks after consuming foods rich in protein. Serum ammonia test revealed hyperammonemia. Genetic tests showed hemizygote c.206A > G (p.Gln69Arg) mutation in OTC gene. The patient is given a protein poor diet which resulted in significant improvement with clinical symptoms and a decrease in nausea and vomiting.
Discussion
Osteoporosis was reported previously in lysinuric protein intolerance which is a member of the family of urea cycle defects[2]. In the present case, OTCD may be a possible cause of osteoporosis. Although the mechanism is not fully understood the low-protein content in diet, the decrease in amino acid activity can cause decreased collagen synthesis, leading to a decrease in bone density[3].
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EP156

Abstract withdrawn

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EP157

The role of osteoprotegerin and sclerostin in bone metabolism in children with congenital adrenal hyperplasia

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Aim
Serum sclerostin levels as an indicator of bone resorption in children with congenital adrenal hyperplasia (CAH) have not been evaluated to date. The aim of this study was to determine the role of osteoprotegerin (OPG) and sclerostin in bone metabolism in children with CAH.
Methods
Thirty-one patients (19 girls, 12 boys) with CAH (aged 11.6 ± 3.7 years) and 31 healthy children (age- and sex-matched) as controls were included in the study. The patients were using glucocorticoids (GC) for at least six months. Serum levels of OPG, sclerostin, calcium, phosphate, alkaline phosphatase, parathormone, and 25-hydroxy vitamin D were assessed in patients and controls. Bone mineral density was measured by dual energy X-ray absorptiometry (DEXA) of the lumbar spine.
Results
In patients with CAH and controls, the mean lumbar spine bone mineral density were 0.841 ± 0.220 and 0.852 ± 0.202 ($P > 0.05$), respectively, and 70% of the patients and 68% of the controls were pubertal. Serum levels of calcium, phosphate, alkaline phosphatase, and parathormone were not found different in the groups ($P > 0.05$). Serum OPG levels of the patients were significantly higher than the controls ($P < 0.001$). Serum sclerostin levels were higher in pubertal patients than the pubertal controls ($p < 0.05$), but there is no significant difference in prepubertal patients and controls ($P > 0.05$). A positive correlation was found between serum OPG and sclerostin levels in patients, while there was a negative correlation between serum OPG and sclerostin levels in controls. Serum 25-hydroxy vitamin D levels of the patients and controls were 19.2 ± 7.5 ng/ml and 14.2 ± 4.8 ng/ml, respectively ($P < 0.05$).
Conclusions
The role of sclerostin in bone metabolism was investigated for the first time in patients with CAH by the present study. Increased OPG levels in the patients were considered as a compensation mechanism against the tendency of increased bone resorption in these patients. As stated in the literature, serum sclerostin levels decreased with increasing age in healthy children, but the expected decrease was not observed in the pubertal period in the patient group. This can be considered as a finding of increased susceptibility to bone resorption in patients with CAH. In addition, the concomitant increase in serum sclerostin and OPG levels in the patients may be associated with increased bone turnover in CAH, especially in the pubertal period.
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EP158

Evaluation of biochemical markers of bone metabolism in patients with secondary hyperparathyroidism and chronic kidney disease

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The diagnostic possibilities of using biochemical markers of bone metabolism in patients with secondary hyperparathyroidism (SHPT) and chronic kidney disease (CKD) have not yet been adequately evaluated. The aim of the study: To evaluate biochemical markers of bone metabolism in patients with various stages of CKD, their relationship with SHPT and bone mineral density.
Materials and Methods
The study included 452 patients with various stages of CKD and 60 persons of the comparison group without CKD aged 20 to 70 years. Serum levels of parathyroid hormone (PTH), vitamin D (25(OH)D), calcium (Ca), phosphorus (P), alkaline phosphatase (AP), osteocalcin (OC), collagen type 1 crosslinked C-telopeptide (CTX) were determined by enzyme immunoassay. Bone mineral density of the lumbar spine (LS), proximal femurs (PF), femoral necks (FN), radius (R), distal part of the radius (R33%) was assessed by double X-ray absorptiometry (DXA). A neural network algorithm for clustering patients was applied to identify a cluster of patients with optimal bone tissue parameters.
Results
The incidence of osteoporosis in patients with CKD ranged from 13.8% in LS, PF, FN to 28.2% in radius. Incidence of osteoporosis increased up to 20% in patients with CKD 4-5. PTH is a major factor of BMD loss in CKD patients, maximum frequency of osteoporosis was noted in patients with SHPT and CKD5. A significant relationship was established between the OC, CTX, ALP and PTH, as well as with the presence of osteoporosis. OC, CTX, ALP progressively increase

with exacerbation of renal failure, which is a consequence of a violation of both bone metabolism and degradation and elimination in conditions of reduced renal function. Population-wide reference intervals OC, CTX are not applicable in patients with CKD 4-5. Using a neural network algorithm, we proposed reference intervals for osteocalcin: CKD 4 - 55-125 pg/ml, CKD 5 before dialysis - 35-235 pg/ml, dialysis - 70-550 pg/ml; for CTX: CKD 4 - 0.3-1.2 pg/ml, CKD 5 before dialysis - 0.7-2.3 pg/ml, dialysis - 0.7-2.5 pg/ml.
Conclusion
The detection of low BMD in patients with SHPT and CKD in some cases requires clarification of bone metabolism. Estimation of OC, CTX, ALP can be used for such purpose. When interpreting the results of the assessment of OC, CTX, the specific reference intervals in CKD 4-5 should be taken into account.

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EP159

Atypical parathyroid adenomas and parathyroid carcinomas: Are there any differences?

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Introduction
Parathyroid carcinoma (PC) is a very rare neoplasm, which has histopathological features different from those of atypical parathyroid adenomas (APA). However, the clinical course of both tumour types is similar, with the exception of the unusual metastases of the carcinoma. With this study we aim to identify those clinical-analytical and anatomopathological variables that allow us to differentiate PCs from APAs.
Material and Methods
Retrospective observational clinicopathological study of a cases series diagnosed with PC and APA in the period 2000-22. The classic histological criteria of invasion of adjacent structures, vascular permeation, perineural infiltration and/or development of metastases were used to diagnose PC. Adenomas with atypical cytoarchitectural features, but without features of invasiveness or metastasis were considered APA. Immunohistochemistry for parafibromin, PGP 9.5 and galectin-3 was performed. Post-surgical tumour recurrence was determined by detection of disease on imaging and/or by elevation of parathormone (PTH) in blood.
Results
A total of 17 patients with a mean age of 59.6 years were studied. 41.2% ($n=7$) were classified as PC, of which one had distant metastases, and the remaining 58.8% ($n=10$) as APA. No statistically significant differences were observed between PC and APA in the variables of age, sex, pre-surgical blood tests [PTH ($P=0.5$) and calcemia ($P=0.5$)], ultrasound characteristics, percentage of post-surgical cure ($P=0.3$) and recurrence of hyperparathyroidism ($P=0.6$). The case of metastatic PC showed no differential histopathological features. Immunohistochemically, 29.4% ($n=5$) showed loss of parafibromin, of which 2 corresponded to APA and 3 to PC. No differences were observed in the expression of PGP 9.5 ($P=0.5$) or galectin-3 ($P=0.7$) between PC and APA. The group of tumours not expressing parafibromin were associated with age (74 ± 13.3 vs 54.36 ± 16.3 years, $P=0.04$), higher frequency of bone fractures (40% ($n=2/5$) vs 0% ($n=0/12$), $P=0.07$), capsular invasion (100% ($n=5/5$) vs 58.3% ($n=7/12$), $P=0.06$), infiltration of adjacent structures (100% ($n=5/5$) vs 33.3% ($n=4/12$), $P=0.05$) and loss of PGP 9.5 expression (80% ($n=4/5$) vs 16.7% ($n=2/12$), $P=0.02$).
Conclusion
No analytical or clinical behavioural differences were observed between PCs and APAs. Interestingly, loss of parafibromin is associated with locally more aggressive tumour behaviour.

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EP160

Primary hyperparathyroidism: A rare form of presentation

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Introduction
Primary hyperparathyroidism (PHPT) is characterized by parathyroid hormone (PTH) overproduction, causing hypercalcemia. The most common cause is a parathyroid adenoma. PHPT most frequently presents as asymptomatic hypercalcemia or with nonspecific symptoms. Less frequently, it presents with the classical manifestations of bone disease and nephrolithiasis. Acute pancreatitis (AP) as the initial manifestation of PHPT has been reported rarely. Hypercalcemia can cause AP by leading to pancreatic calculi and ductal obstruction, and by activating trypsinogen to trypsin, causing pancreatic autodigestion.
Case Report
A 37 year-old man was admitted to the hospital due to AP. Initial tests revealed elevated amylase and lypase levels (164U/l [NR 13-53U/l] and 106U/l [NR 13-60U/l], respectively), hypercalcemia (14.9 mg/dl [NR 8.6-10.2 mg/dl]), hypophosphatemia (1.9 mg/dl [NR 2.5-4.5 mg/dl]) and acute kidney failure. Further investigation showed elevated serum PTH (1241 pg/ml [NR 14-72 pg/ml]), suggesting PHPT. During hospitalization, the patient was treated with IV fluids and pamidronate 90 mg. On discharge, calcemia was 10.3 mg/dl, amylase was 34U/l, lypase was 66U/l and renal function was normal. The patient denied any previous history of bone disease, nephrolithiasis or other symptoms of hypercalcemia. Renal ultrasound excluded kidney stones. To evaluate for the presence of multiple endocrine neoplasia syndromes types 1 and 2, pituitary function, calcitonin and plasma metanephrines were measured, which were normal. 99mTc-Sestamibi scintigraphy identified a 15 mm right inferior parathyroid nodule, therefore the patient underwent right inferior parathyroidectomy. Intraoperative PTH level decreased to 7 pg/ml. Histology revealed a parathyroid adenoma as the etiology of PHPT. The patient was discharged under calcium carbonate and cholecalciferol treatment (6000 mg + 1600UI per day). Laboratory tests in the first postoperative appointment showed normal PTH, calcium and phosphorus values (71 pg/ml, 9.7 mg/dl and 3.2 mg/dl, respectively). Levels remain normal after having suspended calcium and cholecalciferol therapy (59 pg/ml, 9.6 mg/dl and 2.7 mg/dl, respectively). There has been no recurrence of pancreatitis.
Discussion and Conclusions
AP in patients with PHPT is uncommon (estimated prevalence: 1%-13%), however this can be the initial manifestation of PHPT. While hypercalcemia causes under 1% of AP cases, in patients where calcemia is elevated, investigation of endocrine causes such as PHPT should be prompted.It is also important to note that although histology in this case suggested parathyroid adenoma, the patient presented with severe hypercalcemia ($>$ 14 mg/dl) and very high serum PTH ($\geq$ 10-12 times the upper limit of normal), which are potential predictive factors of parathyroid carcinoma (versus benign causes of PHPT). Therefore, close monitoring will be required.

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EP161

Ectopic parathyroid adenoma of the upper jugulo-carotid region

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Introduction
Ectopic location of the parathyroid glands has been described in 10-15% of patients with hyperparathyroidism. Upper cervical localization is exceptional and may be missed by preoperative localization techniques. We report a rare case of parathyroid adenoma of the upper jugulo-carotid region.
Observation
A 41-year-old woman with no notable pathological history presented diffuse osteoarticular pain. Physical examination showed a right superior jugulo-carotid swelling of 3 cm of the main axis, firm, painless and mobile, without any other associated neck swelling. The laboratory workup revealed a serum calcium level of 2.7 mmol/l, an elevated parathyroid hormone level of 1109 ng/ml, and normal renal function. The neck ultrasound showed an oval 32 mm long axis, a heterogeneous upper right jugulo-carotid mass, and a normal thyroid gland. The technetium-99m-MIBI scan showed no hyper-fixation. The cervicothoracic scan showed a mass on the right neck with heterogeneous enhancement. Intraoperative exploration revealed a firm yellowish right jugulo-carotid mass of a 3 cm long axis that was easily dissected. A frozen section examination revealed a

parathyroid adenoma, and this diagnosis was confirmed by the final anatomopathological examination. The postoperative course was marked by the normalization of PTH and improvement in patient quality of life.
Conclusion
The ectopic upper neck location of parathyroid adenomas is exceptional (less than 1% of adenomas). Sestamibi scintigraphy is of major importance help in the location of parathyroid glands but may be negative for the detection of these high cervical adenomas.

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EP162

Sialolithiasis revealing hyperaparthyroidism: A case report

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Introduction
Primary hyperparathyroidism is associated with lithiasis, but this has been universally considered to refer to kidney lithiasis. Sialolithiasis as a comorbidity or result of primary hyperparathyroidism is uncommon. We report a rare case of submandibular lithiasis in a child and discuss the etiological assessment of this condition.
Materials and Methods
We report a rare case of submandibular lithiasis in a child revealing primary hyperparathyroidism.
Results
A 13-year-old child with no previous history was referred for episodes of right painful submandibular swelling evolving for 1 month. Physical examination revealed a firm and mobile right submandibular swelling measuring 3 cm. Upon intraoral examination, a 5 mm hard mass was felt over the right floor of the mouth area. A neck ultrasonography showed a hypoechoic enlarged submandibular gland associated with a 5 mm intracanal stone causing dilatation of the submandibular duct associated with an hyperplasia of the inferior right parathyroid gland measuring 1.5 cm. The phosphocalcic evaluation and parathormone dosage concluded to a primary hyperparathyroidism. The patient had an intra-oral removal of stone under local anesthesia. The spectrophotometric analysis of the stone confirmed its phosphocalcic nature. An excision of the parathyroid adenoma was performed. Histological findings revealed a parathyroid adenoma. The clinical course was marked by clinical and biological improvement.
Conclusion
Salivary lithiasis is common. An etiological investigation is necessary in children and in recurrent forms to identify the possibility of hyperparathyroidism.

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EP163

Evaluation of ultrasonography and 99mTc-sestamibi scintigraphy in the preoperative imaging study in Primary Hyperparathyroidism

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Introduction
Minimally invasive surgery has become the standard surgical procedure in Primary Hyperparathyroidism (PHP). Targeted parathyroidectomy is associated with a shorter operative duration, a lower risk of complications and a greater patient satisfaction. This approach is dependent on precise localization of the abnormal gland. 99mTc-sestamibi scintigraphy and ultrasonography are acceptable imaging modalities to detect parathyroid adenoma prior to operation but discrepancies exist with regard to diagnostic accuracy. 18F-fluorocholine positron emission tomography has shown promise results but its availability is only in a few centres. The aim of the present study was to evaluate the efficacy of 99mTc-sestamibi scintigraphy and ultrasonography in surgery for primary hyperparathyroidism.
Subjects and Methods
This is a retrospective observational cohort study in 117 patients diagnosed of PHP who were operated on between January 2017 and January 2022. There were 28 males and 89 females, age range: 35-87 years. All patients underwent ultrasonography and 99mTc-sestamibi scintigraphy before surgery. Surgical procedure was neck exploration ($n=42$) or selective parathyroidectomy ($n=75$), according to imaging localization. Statistical analyses used SPSSv20.0 software. Approval of the ethics and research committee was obtained for the study.
Results
Demographic, preoperative, interventional and cure data were compared according to ultrasonography and 99mTc-sestamibi scintigraphy results, distinguishing 3 patient groups: concordant $n=68$, discordant $n=26$, negative $n=23$. Gland weight $P=0.03$ in ultrasonography, and gland size in 99mTc-sestamibi scintigraphy ($P=0.02$), but no concomitant thyroid pathology rates, differed significantly between the positive and negative imaging results groups. In the 117 patients, sensitivity was 68% and PPV 81% for ultrasonography, and respectively 74% and 78% for 99mTc-sestamibi scintigraphy. Both modalities were concordant in 68/117 (58%) and in 58 consistent with surgery result (sensitivity 53%). Histopathological analysis showed: 109 adenomas, 1 carcinoma, 5 multiple adenomas. In 2 patients no lesion was shown. In 110 out of 117, calcemia and PTH were normalized one and six months after surgery.
Conclusion
The performance of associated ultrasonography and 99mTc-sestamibi scintigraphy could be the ideal practice to precisely localize parathyroid lesion in patients with PHPT. Combining both techniques can reduce surgical morbidity.

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EP164

Effect of calcium and vitamine D supplementation on parathyroid glands function after total thyroidectomy

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Aim
The purposes of our study are to study the effect of systematic calcium and vitamin D supplementation on parathyroid glands function after total thyroidectomy.
Patients and Methods
We conducted a prospective cohort study, including patients undergoing total thyroidectomy. Patients were randomly divided into two groups: group 1: with prophylactic supplementation (24 patients) and group 2: without prophylactic supplementation (23 patients). For each patient, undergoing total thyroidectomy, the assessment includes Ca; PTH in preoperatively and at day 1 and day 30 on postoperative.
Result
The mean PTH on day1 for group 1 was 12.7 pg/ml $\pm$ 10.7 and 17.4 pg/ml $\pm$ 7.5 for group 2. The difference was not statistically significant ($P=0.09$; Student's T-test for independent sample). The mean PTH at day 30 for group 2 was 23.4 pg/ml $\pm$ 15.7 and 25.7 pg/ml $\pm$ 9.7 for group 1. We did not notice any difference in mean PTH between the two study groups. ($P=0.54$; Student's T test for independent sample)
Conclusion
Calcium and vitamin D supplementation has no inhibitory effect on PTH on D1 and D30 and therefore does not in any case delay the resumption of parathyroid glands function. In addition, it appears in our study that this supplementation improves parathyroid function at 1 month.

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EP165

PFI and WI before and after loading with vitamin D in vitamin D deficient patients

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Aim
To evaluate the change in PFI (Parathyroid Function Index) and WI (Wisconsin Index) after loading with vitamin D in patients with vitamin D deficiency.

Patients and Methods
In 41 vitamin D deficient patients ($25(OH)_2D < 17.16 \pm 6.07$ ng/ml, mean $\pm$ SD) the PFI (PTHxCa devided by P) and the WI (PTHxCa) were evaluated before and after 3 month loading with Vitamin D 50.000 IU per week for the first 6 weeks and 25.000 IU per week for the next 6 weeks.
Results
$25(OH)_2D$ increased significantly ($P < 0.0001$) and PTH decreased significantly ($P = 0.001$) after 3 month loading with vitamin D while serum calcium and phosphorus showed no change ($P = 0.16$ and $P = 0.19$ respectively). PFI and WI decreased significantly after loading from 17.9 ± 8.2 (mean $\pm$ SEM) to 13.3 ± 7.4 and from 20.4 ± 8.3 to 14.5 ± 6.9, $P = 0.001$ and $P = 0.0008$ respectively. Considering a $25(OH)_2D$ level as the best between 20-50 ng/ml and taking as cut-off value of $25(OH)_2D$ 20.2 ng/ml, the analysis showed for the PIF sensitivity 68.3% and specificity 36.6%, and for the WI sensitivity 68.3% and specificity 53.7%.
Conclusion
PFI and especially WI can potentially be used as indicators of adequate vitamin D loading along with a remeasurement of vitamin D considering that most of the commercial Vitamin D assays overestimate its serum levels.

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EP166

Giant parathyroid adenoma: Report of two cases

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Introduction
Primary hyperparathyroidism is a common disease. It is generally caused by a solitary parathyroid adenoma. Adenomas weighing more than 3.5 g are classified as giant. These giant parathyroid adenomas constitute a rare clinical entity.
Patients and Methods
We report two cases of giant parathyroid adenoma observed in our department of otorhinolaryngology and cervicofacial surgery.
Results
Case 1: A 54-year-old woman was referred to our ENT department for the management of recent hypercalcaemia. She had no previous medical history. She complained of mild constipation, muscle weakness, nausea and intermittent abdominal pain for one month. Cervical examination did not find any palpable masses. Biologically, there was severe hypercalcaemia at 5.59 mmol/l and a PTH level of 2268 pg/ml. SPECT-CT revealed a right parathyroid adenoma measuring $6 \times 2.7 \times 2$ cm in the anterior mediastinum with minimal cervical expression. The patient was managed urgently in the intensive care unit with hyperhydration, forced diuresis and bisphosphonates. The patient underwent double team surgery (cervicofacial surgery and vascular surgery). The parathyroid adenoma was successfully removed by a transcervical approach. Final pathology confirmed the diagnosis of a giant parathyroid adenoma. Post-operative management was straightforward. Her serum calcium and PTH levels normalized rapidly. The patient is currently asymptomatic and normocalcaemic.
Case 2: The patient is 70 years old, diabetic, coronary and chronic renal failure(on haemodialysis since 2019). She had been suffering from diffuse bone pain for a year with functional impotence, especially in the two lower limbs. A parathyroid workup revealed a blood calcium level at the upper limit of normal and an elevated PTH level of 1160 pg/ml even after correction of hypovitaminosis D. Scintigraphy found two MIBI-binding sites, one of which is large and projects below the left lower pole. MRI and CT scan found a 4 cm calcified left basicervical mass extending into the upper mediastinum. The patient underwent a subtotal parathyroidectomy with removal of the subthyroidal lower laterotracheal mass. The postoperative follow up was straightforward. The PTH was back to 35 pg/ml on postoperative day 3 with a blood calcium level of 2.05 mmol/l. Pathological examination concluded to a giant parathyroid adenoma associated with hyperplasia of the remaining parathyroids. The evolution was marked by a regression of bone pain.
Conclusion
Giant parathyroid adenomas are usually solitary. Their treatment is surgical but would require medical preparation. The main post-operative complication is hypocalcaemia. Parathyroid carcinoma remains the main differential diagnosis and can only be ruled out by definitive pathological examination.

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EP167

Cholecalciferol supplementation effect on vitamin D metabolism parameters in hospitalized covid-19 patients

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Background
Recent studies demonstrated clinical benefits of cholecalciferol supplementation among COVID-19 hospitalized patients. However, features of vitamin D metabolism in the acute phase of SARS-CoV-2 infection remain unclear.
Aim
to estimate the level of 25(OH)D and 1,25(OH)2D as well as oral bolus cholecalciferol supplementation effect on the dynamic of vitamin D metabolites in hospitalized COVID-19 patients.
Materials and Methods
A total of 44 hospitalized patients with confirmed COVID-19 were included in the randomized single-center open-label study. Patients in the Group 1 ($n = 22$) received cholecalciferol bolus supplementation at a total dose of 100,000 IU on the first and the eighth days of hospitalization. Patients from the Group 2 ($n = 22$) did not receive cholecalciferol supplementation. Serum 25(OH)D and 1,25(OH)2D levels were estimated for each group on the first and the ninth day of hospitalization. There were no differences in demographic, clinical, laboratory and instrumental patientŝ baseline characteristics, as well as in the total dose of concomitant corticosteroid therapy by the 9th day of hospitalization.
Results
On the ninth day of hospitalization 25(OH)D serum level demonstrated the 45.8% rise in the Group 1, while in the Group 2 there was a decrease in the 25(OH)D level by 17.9%. At the same time, dynamic evaluation of the 1.25(OH)2D level did not show any differences between the groups, while pairwise comparison on the first and on the ninth day of hospitalization revealed a significant increase in the active metabolite concentration ($P < 0.001$) in both groups. It was also no significant correlation between the 25(OH)D and 1,25(OH)2 D level at both time points.
Conclusion
Such vitamin D metabolism parameters in the acute period of COVID-19 may be associated with the 1α-hydroxylase activity alteration. Thus, the increase in serum 1.25(OH)2D level despite of vitamin D status dynamic during the hospitalization could be explained either by the COVID-19 course or by the concomitant corticosteroid therapy.

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EP168

Menses-associated decline of serum calcium in hypoparathyroid women

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Some hypoparathyroid women report the appearance or intensification of hypocalcemia symptoms at the time of menses. It is still unknown whether this is the result of premenstrual syndrome or fluctuations in serum calcium levels. Studies have not found a relationship between fluctuations in levels of sex hormones and serum calcium and phosphorus and it appears probable that they affect neuromuscular excitability through a separate mechanism. Alterations in serum calcium levels during the menstrual cycle are not always detected [Graham WP.; Gordan GS.; Loken HF.; Blum A; Halden A (1964). Effect of Pregnancy and of the Menstrual Cycle on Hypoparathyroidism. The Journal of Clinical Endocrinology & Metabolism, 24(6), 512–516. doi:10.1210/jcem-24-6-512. Saha S, Goswami R. Menstruation associated hypocalcemic symptoms and serum calcium in patients with idiopathic hypoparathyroidism. BMC Endocr Disord. 2014 Mar 21;14:28. doi: 10.1186/1472-6823-14-28.]. But in some patients menses-associated hypocalcemic symptoms correlate with a decline of serum calcium [L. E. Mallette. Case Report: Hypoparathyroidism with Menses-Associated Hypocalcemia Am J Med Sci 1992; 304(1):32-37]. I have studied two patients with chronic postoperative hypoparathyroidism who have experienced muscle stiffness, numbness and paresthesia chiefly during menses. It was accompanied with the significant decline (0.20-0.38 mmol/l) of albumin-adjusted calcium levels after onset of menses.
Case 1. Patient B, 18-year-old. An improvement in well-being during menses has been achieved with an increase in the calcium supplementation dose by 500 mg and alfacalcidol by 0.5 mg. The patient was recommended to increase the dose of calcium and alfacalcidol from the 2nd to the 7th day of menses.

Case 2. Patient D, 36-year-old. Patient was prescribed oral contraceptive in the 63/7 regime, and the hypocalcemic symptoms significantly decreased, the level of serum calcium remained stable. Further research is required to determine the mechanism of serum calcium decline and the possible effect of sex hormones on symptoms of hypocalcemia in chronic hypoparathyroidism.

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EP169

Deep vein thrombosis revealing primary hyperparathyroidism

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Introduction
Primary hyperparathyroidism is a common endocrine disease. Its association with inflammatory and thrombotic events was rarely reported in the literature. The pathophysiological mechanisms of this association remain uncertain. Herein, we report a case of hypercalcemia secondary to primary hyperparathyroidism revealed by a deep vein thrombosis.
Observation
A 65-year-old patient was referred to our department for primary hyperparathyroidism. The patient was admitted to the department of internal medicine for a deep vein thrombosis in the left lower limb. On physical examination, he had a body weight of 68 kg, a height of 165 cm, a body mass index of 24.9 kg/m^2, a blood pressure of 12/08 cmHg, and a heart rate of 57 beats/min. Other systemic and regional examinations did not show any abnormalities. Potential causes of vein thrombosis were excluded. Biological investigations showed a total calcium level of 3.3 mmol/l, a phosphorus level of 0.49 mmol/l, a creatinine level of 60.9 mmol/l, a PTH level of 163 ng/l, albumin level of 43 g/l, a 25 hydroxyvitamin D of 20.2 ng/ml, and a calciuria of 0.21 mmol/24 h. The diagnosis of primary hyperparathyroidism was established. Cervical ultrasound and Sestamibi scan showed a left inferior parathyroid nodule measuring 12.5 × 7 mm. Bone mineral density scan revealed osteoporosis. No other complications were observed. The patient was treated with saline intravenous hydration, zoledronic acid, and a therapeutic dose of low-molecular-weight-heparin. Then, he underwent a left inferior parathyroidectomy. The postoperative course was simple with a total calcium level of 2.25 mmol/l.
Discussion
Thrombotic events were reported in a few patients with primary hyperparathyroidism. This association may be explained by direct activation of prothrombotic factors and hemoconcentration. Even though hypercalcemia is a rare cause of thrombotic events, it should be considered in the clinical evaluation of patients with deep vein thrombosis in the absence of evident causes.

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EP170

Brown tumors complicating hyperparathyroidism

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Introduction
Brown tumor or osteitis fibrocystica is a benign bone lesion reflecting an abnormality of bone metabolism in the context of hyperparathyroidism. It can affect the entire skeleton, including the pelvis, ribs, clavicles and extremities. Involvement of the maxillary bone is very uncommon. We present a case of multiple brown tumors with an unusual maxillo-mandibular localization, revealed by a disorder of phosphocalcic metabolism and tertiary hyperparathyroidism. This case reminds us of the difficulty to establish a correct diagnosis in patients with an osteolytic process of the maxilla and the necessity to look for hyperparathyroidism in front of a giant cell lesion given the insidious character of this endocrinopathy.
Observation
32 year old female patient with the following history
– Chronic kidney disease at dialysis stage
– HTA under ARB II
– Viral hepatitis C
– Left femoral per trochanteric fracture
History of the Disease
The history of the disease began 2 years ago with the appearance of a maxillo-mandibular bone tumor that had been surgically resected with a brown giant cell tumor at the anapath, and whose etiological exploration revealed hyperparathyroidism:
• PTH 668 pg/ml (11×N) and normocalcemia 99 mg/l
• Localization test : a right parathyroid nodule of 17 mm on CT scan
The patient was operated, the procedure consisted in a para thyroidectomy with simple postoperative course and the result of the anapathy was a parathyroid hyperplasia.
Nevertheless, the evolution was marked by the recurrence of her maxillomandibular tumor, which progressively increased in volume, reaching facial deformation and oral obstruction, making feeding difficult.
With a probable tertiary hyperparathyroidism
• PTH more than 20×N and normocalcemia at 98 mg/l
• MIBI scintigraphy with pathological parathyroid of the posterior inferior face of the left lobe of the thyroid.The patient was referred to our training for further treatment. Functionally she shows a deep asthenia.
Clinical Examination
Voluminous mass of the facial mass, painless on palpation, obstructing the oral cavity and causing a tooth separation and intermittent gingivorrhagia. Painless right tibial bone swelling on palpation causing no functional impotence. We are faced with a biologically confirmed hyperparathyroidism initially secondary to kidney failure which has become autonomous with the appearance of a parathyroid nodule marking the transition to tertiary hyperparathyroidism.
Conclusion
The diagnosis of hyperparathyroidism avoids the need of surgery for brown maxillary tumors that should regress after removal of the parathyroid lesion.

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EP171

Approach to a Mediastinal Parathyroid adenoma: A case report

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Ectopic mediastinal parathyroid adenoma is a rare cause of primary hyperparathyroidism (PHPT), which is reported in 1-1.5% of patients. We present you a case of a 22-year old male, who was suffering from severe itchiness which significantly interferes with his daily activities of life. His laboratory results were suggestive of PHPT (Table 1). His initial scans, including Technetium-99m (Tc-99m) Sestamibi (Mibi) did not reveal any abnormality. Subsequently, increase of PTH level along with new onset nausea and fatigue were observed, due to which further investigation was required. His neck and head Ultrasonography (USG) was normal. Second Tc-99m Mibi illustrated an anterior mediastinal mass in the thymic area with focal atypic activity, which is suggestive of a potential ectopic parathyroid adenoma. To accurately localize the adenoma, choline Positron Emission Tomography-Magnetic Resonance Imaginging (PET-MRI) and choline PET-Computer Tomography (CT) were ordered. The images of PET-CT were correlating with the data obtained from the parathyroid scintigraphy. It is recommended to perform parathyroidectomy to PHPT patients, who are diagnosed at 50 years or younger regardless of existence of other surgery indications. Consequently, the patient underwent parathyroidectomy and left thymectomy. Histopathological examination has confirmed the diagnosis. His follow-up blood results were within normal limits and symptoms were resolved (Table 1). The most challenging aspect of the management of PHPT is establishing the accurate localization of the hyperfunctioning adenoma. In addition to that, localization has a huge impact on the success of parathyroidectomy. Although there are many techniques such as USG, Tc99m-Mibi, parathyroid four-dimension CT, PET and MRI, no universally recommended algorithm exists. The most commonly used method is concordant application of USG and Tc99m-Mibi. The reported case had been succesfully treated following useage of Tc99m-Mibi and choline PET-CT to establish the accurate location of the adenoma. We strongly believe that our approach with a multimodality imaging strategy provides valuable information to the physicians.

Table 1 Pre- and post-operative laboratory values

Dates	PTH (pg/ml)	Total calcium (mg/dl)	Phosphorus (mg/dl)	Calcium excretion in 24 hours urine collection (mg/day)
31.07.2021	206.3	11.1	3.28	N/A
26.08.2021	145.8	11.29	2.54	474
12.10.2021	49.4	10.76	3.54	N/A
16.09.2022	61.6	10.17	3.18	N/A

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EP172

Epidemiological characteristics of cardiovascular diseases in primary hyperparathyroidism according to the Russian Registry

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Objective
Primary hyperparathyroidism (PHPT) is associated with a higher incidence of different cardiovascular diseases (CVD), but the prevalence of CVD in PHPT remains unclear.
Aim
To evaluate the prevalence of CVD in PHPT according to the RussianPHPT Registry.
Materials and Methods
The Registry includes a database of patients with PHPT available at the Endocrinology Research Centre (Moscow) since 2007, which was transferred to the online platform in 2017. New cases of the disease, as well as dynamic monitoring, are recorded through an electronic form by medical professionals. The data of the included patients were entered into the register by 247 endocrinologists from 81 regions of the Russia. Data are given as medians, unless otherwise noted.
Results
Data from the Registry was uploaded on September 1, 2022. The study included 4892 patients with PHPT. 2308 (47.2%) of them had their cardiovascular history filled in. Among them the most frequent cardiovascular complication was arterial hypertension (AH) (up to 96%), while left ventricular hypertrophy was present in 5.8% of patients. A history of coronary artery disease (CAD) was diagnosed in 20.1%, calcification of the structures of the heart and/or blood vessels was observed in 2.7% of patients. Patients with a mild course of PHPT were significantly younger (62 vs 68 years, $P<0.001$) and had lower concentrations of parathyroid hormone (PTH) (118 vs 141 pg/ml, $P<0.001$) , total calcium, (2.67 vs 2.75 mmol/l, $P<0.001$) and higher GFR (84 vs 76 ml/min/1.73 m^2) than patients with symptomatic PHPT. In patients with mild PHPT, the frequency of CVD was significantly lower than in the patients with symptomatict PHPT: for all CVD 37.9 vs 46%, $P<0.001$, for AH 36.5 vs 51.6%, $P<0.001$ and for ischemic heart disease 4.4 vs 11.9%, $P<0.001$, respectively. Patients with AH were statistically significantly older, had higher serum PTH levels (149 vs 138 pg/ml), and lower GFR compared with normotonic patients. Patients with CAD were also older than those without CAD and had higher ionized calcium levels(1.4 vs 1.37 mmol/l, $P=0.006$), and lower GFR.
Conclusion
There is a high incidence of CVD in PHPT. The severity of PHPT is associated with higher incidence of all CVDs but most often with AH and ischemic heart disease in particular.

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EP173

The effect of Immune Checkpoint Inhibitors (ICIs) in Bone Metabolism: A case series analysis

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Background
Immune checkpoint inhibitors (ICIs) constitutes a novel treatment for patients with melanoma. Endocrine-related adverse effects are now a distinctive clinical entity of ICIs, with hypophysitis and thyroiditis being the most common. Recent consensus doesn't suggest routinely screening of bone mass indexes in patients on ICIs since data in the literature are scarce.
Methods
Data regarding bone disease were retrospectively analysed in 118 patients with melanoma treated with ICIs who were referred to our unit for endocrine-related adverse events. Only patients with available data of bone density in two sites (left femoral bone and lumbar spine), as defined by Dual energy X-ray absorptiometry (DXA) before as well as after ICIs treatment were included in the study. Biochemical markers associated to bone remodelling such as calcium, phosphorus, alkaline phosphate, 25-OH vitamin D and parathormone levels were also registrated. Ten-year probability of fracture score (FRAX score) adapted to Greek population was also calculated. DXA was assessed at least one year post-ICIs interruption (median follow up: 2.5 years).
Results
Six patients (all females, median age: 70.5 years) fulfilled the criteria of inclusion in this case series. Five patients had been treated with systemic monotherapy with an anti-PD1 agent (nivolumab ($n=4$) or pembrolizumab ($n=1$)). The last patient had received combination therapy with anti-PD1 plus anti-CTLA4 (nivolumab plus ipilimumab) therapy. At baseline before any treatment, 2 (33.3%) patients presented with normal bone density, 3(50%) with osteopenia and the last one (16.6%) with osteoporosis treated with calcium replacement and bisphosphonates (ibandronic acid). Baseline levels of biochemical bone metabolism markers were within the normal range except for 25 OH vitamin D levels which was deficient in all 6 patients necessitating the initiation of replacement with cholecalciferol with a median dose of 2000 units administered daily. No bone fracture was diagnosed radiologically during ICIs treatment. None of the patients presented any difference in the T score, the BMD or the FRAX score during the follow-up post- ICIs treatment.
Conclusions
Bone disorders are rarely searched in patients treated with ICIs thus data in the literature are rare. Our case series analysis showed no difference of T score, BMD levels or of the FRAX score in 6 patients with melanoma before and after receiving ICIs in a median follow up of 2.5 years. No osteoporotic fracture was detected neither. Further large-scale analyses with longer follow-up are required in order to assess the effect of ICIs on bone metabolism.

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EP174

Predictive factors of Hungry Bone Syndrome after surgical management of Primary Hyperparathyroidism

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Introduction
Primary hyperparathyroidism (PHP) is a common endocrine disease, and its most effective treatment is surgery. Hungry bone syndrome (HBS) is one of the complications that can occur after parathyroidectomy, and that can cause severe and prolonged hypocalcemia. The aim of this study was to determine the risk factors for HBS in patients who underwent parathyroidectomy for PHP.
Patients and Methods
This is a retrospective descriptive and analytic study of 48 patients with primary hyperparathyroidism followed-up in the Endocrinology-Diabetology and Nutrition Department of the University Hospital Center of Mohammed-VI-Oujda in Morocco, from which 36 patients underwent parathyroidectomy, and were included in this study.
Results
Out of the patients included in the study, 3 cases (8.3%) had HBS, and 33 cases (91.7%) didn't develop HBS. Compared to patients who didn't have this complication, these patients had a lower age (43.33 ± 16 vs 54.6 ± 10.7 years). A feminin predominance was observed in both groups. The preoperative biological analysis demonstrated: higher serum levels of calcium (135.4 ± 8.2 vs 120.1 ± 27.4 mg/l), of PTH 1-84 (1423 ± 1209.6 vs 413.56 ± 379.5 pg/ml), of ALP (436.2 ± 281.6 vs 178.61 ± 103.9UI/l) and lower levels of phosphorus (16.7 ± 1.5 vs 21.57 ± 5.9 mg/l) and of vitamin D (6.3 ± 1.7 vs 11.8 ± 6.3 ng/ml) in the HBS group. A significant association was found between higher preoperative levels of ALP ($P=0.04$) and PTH 1-84 ($P<0.001$) and the occurrence of HBS. Cervical ultrasound showed no difference in number of adenomas between the 2 groups (1 localisation). Bone densitometry indicated osteoporosis in the 3 cases of HBS.
Conclusion
Based on these readily obtainable parameters and the results of our study, higher preoperative ALP and PTH 1-84 levels, were significantly associated with a greater risk of development of the hungry bone syndrome following parathyroid surgery.

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EP175

Electronic health record with decision support as a tool to improve quality of care for women with postmenopausal osteoporosis

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Background and Aims
Awareness and knowledge about any disease is the first step to prevent and treat it. Osteoporosis is a worldwide health problem. Osteoporosis is characterized by decreased normal bone density. More than 8.9 million fractures worldwide annually are caused by osteoporosis; these fractures are a significant cause of morbidity and mortality. Evidence suggests that the modification of several lifestyle habits, diagnostics, prevention and treatment could assist in lowering the incidence of osteoporosis. The aim of our study was to explore the quality of osteoporosis care experienced by women in Russia in Fomin Clinic in 17 cities in Russia and how it could be improved with the help of Electronic Health Record with decision support.
Methods
244 Electronic Health Records of women aged 56.4 before and after the start of the decision support (52 и 54 respectively) were analyzed and rated on a 100-point scale(diagnostics using FRAX and dual-energy x-ray absorptiometry (DXA) (lumbar spine and hip), nutrition, physical activity, drugs recommendations were evaluated by both experts and artificial intelligence). The decision support system based on Guidelines of Russian Association of Osteoporosis, National Osteoporosis Foundation and Endocrine Society.
Results
The average score before using decision support was 43, and after doctors started to use it the average score after 6 months of using became 81.
Conclusions
Electronic Health Record with decision support is great tool wich improves quality of care for postmenopausal women and refines the diagnosis and treatment of osteoporosis in different cities in Russia.

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EP176

Hypophosphatasia: recurrent fractures and a suppressed alkaline phosphatase level - can we make the connection?

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Case
A 66-year-old female was referred to the Endocrinology clinic for suspected osteoporosis after a right femoral shaft fracture. As the site was atypical and the injury was low energy, a pathological fracture was suspected. There was a history of recurrent fractures sustained after the age of 30 years and were either spontaneous or from low-energy impacts (Table 1). Growing up, she was told that "there was something wrong with her bones" and required regular physiotherapy. She reported having a "funny" walk and the inability to run. She also described life-long myopathic symptoms. She could only walk for 10-15 yards with a stick before needing to rest. She took paracetamol and a buprenorphine patch for chronic pain and was on doxazosin and losartan for hypertension. She underwent a left hemiarthroplasty for NOF and an intramedullary nail to fix the right femoral shaft fracture. Her mother suffered recurrent fractures. Her grandson was diagnosed with a skeletal deformity in utero, which was deemed incompatible with life. Apart from a waddling gait, there were no clinical abnormalities. The relevant initial blood tests are listed in Table 2. Myeloma screen, tumour markers and creatine kinase were normal. Interestingly, the ALP was suppressed (chronically) with normal calcium and vitamin D and raised phosphate levels. DEXA scan was inconclusive due to spinal degeneration and metalwork in both hips. Congenital osteopathy was suspected, and a genetic screen revealed compound heterozygosity for pathogenic variants c.400_401delinsCA (p.Thr134His) and c.571G>A (p.Glu191Lys) in the HPP gene confirming ***Hypophosphatasia***.
Outcome
Vitamin D and physiotherapy were commenced, and she was accepted for Asfotase alfa therapy in a specialist metabolic bone clinic.
Learning points:
• Hypophosphatasia results from mutation(s) in the tissue non-specific ALP encoding gene with reduced activity of ALP and defective mineralisation of bone and teeth.
• Suspect hypophosphatasia in cases of recurrent fractures, myopathic symptoms, poor dentition, and suppressed ALP in the presence of normal calcium levels, especially if there is a family history of skeletal problems.

Table 1 Fracture history.

Fracture
Right elbow
Sternum
Left foot
Left ulna
Left neck of femur (NOF)
Left humerus
Right femoral shaft

Table 2

Blood test	Result	Normal range
Parathyroid hormone	3.1 pmol/L	1.6-6.9
Thyroid-stimulating hormone	1.8 mU/L	0.55-4.8
Adjusted calcium	2.37 mmol/L	2.2-2.6
Phosphate	1.8 mmol/L	0.8-1.5
Bilirubin	9 mol/L	<21
Alanine aminotransferase	47 IU/L	0-34
Alkaline phosphatase (ALP)	5 IU/L	30-130
Vitamin D	75 nmol/L	>51
Prolactin	338 mU/L	59-620

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EP177

Maxillary brown tumor revealing primary hyperparathyroidism: A case report

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Introduction
Primary hyperparathyroidism is an asymptomatic endocrine disorder in 80% of the cases. The bone manifestation represents the late stage of the disease and the brown tumor represents an exceptional and rare lesion.
Observation
We report the case of a 73-year-old patient, with a medical history of type 2 diabetes, followed in the oto-rhino-laryngology department for a gingival tumor. A biopsy was performed and the anatomopathological examination was in favor of a reparative granuloma. She was referred to our department for further exploration. The calcium phosphate balance showed an hypercalcemia at 3.37 mmol/l, an hypophosphatemia at 0.53 mmol/l and a high PTH at 451 pg/ml, suggesting primary hyperparathyroidism. The thyroid ultrasound showed no parathyroid nodules, with suspicious adenopathies and the parathyroid scintigraphy revealed a lower right parathyroid adenoma. Complementary thoraco-abdomino-pelvic CT scan revealed two retro-thyroid masses (left 34×16×53 mm and right 29×16 mm) with a lytic lesion type Ib Lodwick of the left iliac bone of 19 mm corresponding to a second brown tumor. As for the assessment of the complications of the hypercalcemia; the electrocardiogram showed a regular sinus rhythm at 60 bpm without shortening of the QT interval, the bone densitometry did not find osteoporosis and the renal ultrasound did not show any lithiasis. The patient was proposed for parathyroid surgery.
Discussion
Nowadays, it is rare that a brown tumor of the maxilla is the circumstance of discovery of hyperparathyroidism. But this lesion must always lead to a calcium level assessment, because the treatment is etiological and the tumors regress spontaneously after parathyroid surgery.

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EP178

Development of parathyroid adenoma suggesting tertiary hyperparathyroidism in a patient with a renal transplant history

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Introduction
Tertiary hyperparathyroidism (THPT) is not uncommon in patients with secondary hyperparathyroidism after successful renal transplantation. It occurs

up to 25% of these patients one year after transplantation despite renal function improvement. It can be developed due to the autonomous function of at least one parathyroid gland and leads to overproduction of parathyroid hormone (PTH). Tertiary hyperparathyroidism mostly reveals diffuse or nodular pattern of chief cell hyperplasia of the parathyroid glands which eventually leads them to adenomatous transformation. The THPT results in significant metabolic complications and symptoms, especially in patients who have had kidney transplants and are taking immunosuppressive therapy. Related symptoms include pruritus, severe osteodynia, pathologic fractures, memory loss, concentration difficulties and feelings of depression.
Case Report
A 35-year-old female who was known to have secondary hyperparathyroidism and a history of renal transplantation was admitted to our hospital due to hypercalcemia on routine blood tests. The patient underwent superior and inferior right parathyroidectomy and left inferior parathyroidectomy. Histological examination showed an adenoma measuring 3.6 cm. of the right inferior parathyroid gland and hyperplasia of the left inferior and right superior parathyroid glands, suggesting THPT. The level of serum and serum calcium were normalized after the surgery.
Conclusion
Patients with THPT commonly have significant symptoms and metabolic complications that improve after parathyroidectomy. Parathyroidectomy is the current recommended intervention to cure the disease. Successful surgical treatment results in a dramatic reduction in PTH levels and improvement of clinical symptoms especially bone pain. It is also associated with better patient survival. However, Cinacalcet is an alternative medical treatment for subgroup of patients in whom surgery is deemed inappropriate. Determining the optimal treatment for the individual patient is challenging for nephrologists and endocrine surgeons.

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EP179

Primary hyperparathyroidism by an ectopic mediastinal subpericardial parathyroid adenoma

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Introduction
Primary hyperparathyroidism is frequent; it can be ectopic in 11 to 25% of cases, the mediastinal position is the most frequent ectopic position, but the intrapericardial position is exceptional.
Clinical Case
A 58 year old woman with primary hyperparathyroidism complicated by severe osteoporosis. The CT scan and parathyroid scintigraphy reveals a 17 mm parathyroid adenoma in the mediastinal aortopulmonary position. After a first thoracic surgery which was unsuccessful, the patient was treated with injectable then oral bisphosphonates, while waiting for the second surgery done after two years, a second surgery was performed with extirpation of an adenoma between the ascending aorta and the trunk of the pulmonary artery, after opening the pericardium under the aorta. After surgery the patient developed signs of hypocalcaemia immediately after surgery, PTH dropped by more than 50% (from more than 200 to 99 pg/ml), the histological study was in favor of an ectopic parathyroid adenoma. The evolution was marked by a normalization of the phosphocalcic balance.
Discussion
Among the ectopic forms of hyperparathyroidism, the intrapericardial position of a parathyroid tissue is exceptional and difficult to operate, hence the need to entrust the patient to an experienced surgeon.

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EP180

Vitamin D in Primary Hyperparathyroidism: status and its effects on Primary Hyperparathyroidism

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Introduction
Low levels of vitamin D are commonly seen in patients with primary hyperparathyroidism (PHP). The aim of this study was to determine the vitamin D status and to evaluate its relation with primary hyperparathyroidism severity.
Patients and Methods
This is a retrospective descriptive study including 48 patients with primary hyperparathyroidism followed-up in the Endocrinology-Diabetology and Nutrition Department of the University Hospital Center of Mohammed-VI-Oujda in Morocco. Clinical, biochemical, and densitometric presentation, were compared among patients with vitamin D insufficiency (group 1) and deficiency (group 2).
Results
The mean age of our patients was 55.60 $\pm$11.4 years, with a clear female predominance (77% of cases). The average vitamin D level was 12.06$\pm$7.4 ng/ml, 18 cases (37.5%) had vitamin D insufficiency, and 29 cases (60.4%) had vitamin D deficiency, while only one case (2%) had normal level of vitamin D. The discovery of primary hyperparathyroidism was mainly by an incidental finding of hypercalcemia in these patients. Bone densitometry indicated osteoporosis, osteopenia, and was normal in 53.12%, 28.12% and 18.75% of cases respectively. Ten percent of patients had renal failure, and 35.6% had urolithiasis as complications. We observed that patients who had vitamin D deficiency had higher levels of serum calcium (134.06 $\pm$ 25.60 vs 118.57$\pm$21.31), and PTH 1-84 (468.05$\pm$536 vs 362.04$\pm$432.9) comparatively to those who had vitamin D insufficiency. Also, urolithiasis was twice as common in those with vitamin D deficiency. Post-operative severe hypocalcemia was only seen in those who had vitamin D deficiency before surgery. Therefore, no difference in clinical presentation and severity, in bone mineral density, and the prevalence of renal failure were noted between the two groups.
Conclusion
Vitamin D deficiency worsens the profile of hyperparathyroidism. For this reason, a systematic preoperative screening is necessary in order to prevent its complications.

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EP181

Late-onset hypoparathyroidism following total thyroidectomy

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Background
Post-operative hypoparathyroidism is a known complication of total thyroidectomy. It can either be transient or long-term requiring lifelong treatment. Delayed presentation of hypoparathyroidism occurring after several years of surgery is rare, with only a few cases reported in literature but can be life-threatening.
Presentation
We report a case of a 70-year-old female presenting with features of hypocalcaemia (tinnitus and tingling in her fingertips) that required hospital admission. Following were her blood.
Results–
She was treated with IV calcium gluconate, and subsequently discharged with Calvive 1gm OD and Alfacalcidol 0.5 mg BD and followed up in the metabolic bone clinic. She had a total thyroidectomy for a multinodular goitre 12 years ago, wherein she developed transient hypocalcaemia in the immediate post-operative period which resolved spontaneously. Therefore, a diagnosis of late-onset hypoparathyroidism following total thyroidectomy was confirmed.
Discussion
Hypoparathyroidism causes hypocalcaemia, hyperphosphatemia and generally has very low or undetectable PTH levels. In our case, her PTH was "normal" likely due to the remaining parathyroid tissue compensating for hypocalcaemia. Late-onset hypoparathyroidism is rare, but a few cases have been reported previously. It is likely caused by either progressive atrophy of the parathyroid glands, scar tissue formation leading to hypovascularization and progressive ischaemia, or arteriosclerotic changes leading to infarction or atrophy of the remaining parathyroid tissue. British Association of Endocrine and Thyroid Surgeons (BAETS) guidelines advise checking calcium levels within 12 hours postoperatively, but there was minimal guidance found on whether calcium levels need to be re-checked annually. Although our patient was relatively well, there have been cases reported where patients present with seizures due to late-onset hypoparathyroidism.

Tests	Results	Normal reference range
Adjusted calcium	1.75 mmol/l	2.20 - 2.60 mmol/l
Phosphate	1.61 mmol/l	0.80 - 1.50 mmol/l
25-hydroxy Vitamin D	57 nmol/l	50–120 nmol/l
PTH	1.8 pmol/l	1.6-6.9 pmol/l
Magnesium	0.85 mmol/l	0.7–1.0 mmol/l
eGFR	89 ml/min/1.73 m^2	

Conclusion
In patients with a history of thyroidectomy, we recommend an annual blood test for bone profile and PTH along with a thyroid function test.

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EP182

Brown tumors in patients with secondary and tertiary hyperparathyroidism

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Introduction
Brown tumors result from the destruction of bone occurring especially in regions where bone resorption is rapid with hemorrhage and repa-rative granulation tissue replacing the normal tissue. This bone lesion can affect any part of the skeleton. It results from uncontrolled hyperparathyroidism in patients with chronic renal failure.
Objective
The aim of this report is to describe the management and the evolution after treatment of brown tumors in patients with chronic renal failure.
Method
This is a retrospective study including 5 patients with chronic renal failure who developed brown tumors due to secondary or tertiary hyperparathyroidism. This study was carried out from 2008 to 2022.
Results
The average age was 38 years predominantly males (sex ratio (M/F) = 1.5). The tumor was located in: the mandible (1 case), the maxilla and the mandible (1 case), the sternum (1 case) and the femora (2 cases). The mean serum calcium level was 1.90 mmol/l. The mean phosphoremia level was 2.20 mmol/l. The mean PTH level was 1500 pg/l. All patients had subtotal parathyroidectomy. Histologic examination of the gland showed parathyroid hyperplasia in all cases. No patient underwent intervention on the tumor. The evolution after surgery was favorable in all cases, with clinical and radiological stabilization of bone lesions in 2 cases and spontaneous regression without recurrence in 3 patients.
Conclusion
Patients with chronic renal failure may develop brown tumors in advanced stages of the disease as a result of uncontrolled hyperparathyroidism. Treatment is based on reducing the levels of PTH, either through medical management, or surgery.

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EP183

Severe hypocalcemia during respiratory alkalosis reveals a case of Pseudohipoparathyroidism type 1B

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We present a case of Inactivating PTH/PTHrP signalling disorder (IPPSD) revealed in aduthood in the context of respiratory alkalosis caused by covid-19 infection that led to worsening of the preexisting hypocalcemia and intensification of the usual hypocalcemic symptoms. A 39 year old female with history of subclinical hypothyroidism and bilateral cataracts was admited due to hypoxemia in the context of severe covid-19 infection with bilateral pulmonary infiltrates. She was visiting a Neurologist because of chronic complaints of tingling and cramping, with no visible pathology on the exams so far performed (apart from the basal ganglia calcifications on the brain CT from 2010). On admission she was hypotensive, tachypneic, feverish and complained of paresthesia and acral cramping. Metabolic alkalosis (pH 7.48, pCO2 31 mmHg, pO2 62 mmHg, K^+ 2.97 mmol/l, Na^+ 133 mmol/l, Ca^{2+} 0.5 mmol/l) worsened the eletrolyte imbalance leading to severe symptomatic hypocalcemia with prolongued QT segment (500 ms) on the ECG. The initial calcemia (Ca^{2+}) was 3.9 mg/dl [8.6-10], P (Phosphate) 4.0 mg/dl [2.5-4.5], 25OH-vitamin D 13 ng/ml, Mg 1.8 mg/dl [1.6-2.6], 1.25(HO)2 vitamin D was normal, PTHI 190 pg/ml [15-65]. After 48 h Ca^{2+} was 6.4, P 6.1, 25OH-vitamin D 18 ng/ml; the patient was discharged with Ca^{2+} of 9.2, P 4.5 and 25OH-vitamin D of 24 ng/ml with the suspition of IPPSD given the protracted history of paresthesia, cataracts and intracerebral calcifications sugesting long standing hypocalcemia. During follow up PTHi ranged 190-347 pg/ml [15-65], Ca^{2+} 6.1-9.2 mg/dl, P 2.7-5.1 mg/dl, 25OH-vitamin D 21-34 ng/ml and she remained assymptomatic and compliant with calcitriol 0.5 mg q12 h, 1500 mg of calcium carbonate 5 times daily and 22400UI colecalciferol montly. Thyroid antibodies were negative and the US normal; the TSH maintained the same subclinical pattern fluctuating from 3 to 8.8 mUI/l. The gonadal axis were not afected. The patients has a BMI of 32 kg/m^2 though it is not possible to confirm if obesity started at a young age. Hand X-ray showed no brachydactily nor subcutaneuous ossification. Given the clinical suspition for Pseudohipoparathyroidism type 1B, GNAS sequencing was performed but no mutation was found. Nevertheless this clinical IPPSD subtype is more often associated with metilation errors so genetic examination was performed with metilation probes and the genetic mutations were identifyed. Clinical and biochemical manifestations are usually unnoticed during childhood; diagnosis is often delayed owing to lack of recognition of the syndrome. Genetic counseling may facilitate the diagnosis at an early age and prevent the patients from misleading follow-ups or diagnosis and/or engaging extensive unnecessary investigations.

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A case of a giant parathyroid adenoma associated with a secondary hyperparathyroidism in a hemodialysis patient

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Introduction
Secondary and tertiary hyperparathyroidism (HPT) usually result from parathyroid gland hyperplasia that produces excess parathyroid hormone (PTH). Collectively, secondary and tertiary HPT comprise a minority of the patients diagnosed with HPT. Due to the relative rarity of these conditions and common underlying disease pathology, they are frequently discussed and researched together. While the disease processes are related, secondary and tertiary HPT are two distinct and separate entities.
Patients and Methods
We report a case of a giant parathyroid adenoma associated with a secondary hyperparathyroidism in a hemodialysis patient observed in our department of otorhinolaryngology and cervicofacial surgery.
Observation
The patient is 70 years old, diabetic, coronary and chronic renal failure, and has been on haemodialysis since 2019. She had been suffering from diffuse bone pain for a year with functional impotence, especially in the two lower limbs. A parathyroid workup revealed a blood calcium level at the upper limit of normal and an elevated PTH level of 1160 pg/ml even after correction of hypovitaminosis D. Scintigraphy found two MIBI-binding sites, one of which is large and projects below the left lower pole. MRI and CT scan found a 4 cm calcified left basicervical mass extending into the upper mediastinum. The patient underwent a subtotal parathyroidectomy with removal of the subthyroidal lower laterotracheal mass. The postoperative follow up was straightforward. The PTH was back to 35 pg/ml on postoperative day 3 with a blood calcium level of 2.05 mmol/l. Pathological examination concluded to a giant parathyroid adenoma associated with hyperplasia of the remaining parathyroids. The evolution was marked by a regression of bone pain.
Conclusion
Tertiary HPT is classically caused by hyperplasia of all four glands, though some reports indicate that over 20% of patients may have single or double adenomas as the underlying pathology. Management is essentially based on surgical treatment.

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Comparison of biochemical values in asymptomatic and symptomatic urolithiasis

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Background
Primary Hyperparathyroidism (PHPT) is a common endocrine disorder that is characterized by hypercalcaemia and elevated or inappropriately normal serum levels of parathyroid hormone. Most often, the presentation of PHPT is asymptomatic. PHPT can manifest with osteoporosis and hypercalciuria as well as with vertebral fractures and nephrolithiasis, both of which can be asymptomatic. Our aim in this study; to determine the frequency of kidney stones in patients operated for primary hyperparathyroidism and to compare the biochemical values of symptomatic and asymptomatic patients with kidney stones.
Methods
It was planned to include patients who had undergone parathyroidectomy, who applied to Ankara Yıldırım Beyazıt University Atatürk Training and Research Hospital between December 2006 and January 2019 and to Ankara City Hospital Endocrinology and Metabolic Diseases Clinic between February 2019 and November 2021.
Results
Of 886 patients who were operated for primary hyperparathyroidism, 15.9% (n: 141) were male. 189 (%21.3) patients had symptoms at the time of diagnosis. Diffuse body pain (37%), flank pain (22.2%), fatigue (11.6%), dyspepsia (6.9%), polyuria and polydipsia (4.2%) were the most common symptoms. Of the patients, 45.6% (*n*:388) had osteoporosis, 24.6% (*n*:253) had osteopenia, and 30.3% (*n*:257) kidney stones. Urinary symptoms were present in 133 (16.5%) patients. Genetic analysis was performed on 83 patients. 7.2% of the patients who underwent genetic analysis were men-1. The mean age of the patients was 53.6±11.9 (18-85) years. The mean preoperative total calcium of the patients was 11.1±1.1 (6.3-18.6) mg/dl. The mean preoperative phosphorus was 2.6±0.7 (0.7-9.0) mg/dl. The mean preoperative 24-hour urinary calcium of the patients was 380.5±198.2 (24-1438) mg/24-hour. The mean preoperative 24-hour urine phosphorus was 797.9±350.4 (30.2-3798) g/24 hour. 257 patients with kidney stones were divided into two groups according to urinary symptoms. 70.2% (*n*:92) of 131 patients with urinary symptoms and 82.7% (*n*:91) of 110 patients without urinary symptoms were women. The proportion of women was significantly higher in the group without urinary symptoms (*P*:0.035). The median age was significantly higher in the group without urinary symptoms compared to urinary symptoms group (54.7 years vs 51.5 years, *P*:0.039). osteoporosis rate, total calcium value, phosphorus value, parathormone value, 24-hour urinary calcium and 24-hour urine phosphorus value were similar for the two groups.
Conclusion
Patients with symptomatic nephrolithiasis were younger and more male dominated.

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A rare etiology of primary hyperparathyroidism

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Introduction
Parathyroid cysts are a rare clinical and histological entity, with less than 300 cases reported in the literature. They constitute 0.5% of all parathyroid pathologies and 1% of all cystic lesions in the cervical region. Parathyroid cysts can give rise to a varied symptomatology by the local or hormonal repercussions.
Case
We report the case of a 65-year-old patient with no pathological history who presented for bone pain with functional impotence of the lower limbs. Cervical examination noted a right basicervical tumefaction of 1.5 cm that is firm and mobile on swallowing. The biological assessment objectified an hypercalcemia at 2.43 with an hyperparathyroidism at 2406 pg/ml. Ultrasound evocated 2 necrotic lower lobe thyroid nodules. The parathyroid scintigraphy doesn't show any fixation. Cervical scan showed a cystic lesion at the level of the lower part of the right thyroid lobe and another heterogeneous one on the left side. A para thyroidectomy of the lower right parathyroid gland, which had a large cystic component, was performed associated with left para thyroidectomy. Histopathological examination revealed a right lower parathyroid cyst with hyperplasia of the parathyroid parenchyma of both parathyroid glands. Postoperative follow-up showed a normalization of the calcium and parathyroid hormone levels.
Conclusion
Parathyroid cycts often involved the lower parathyroid glands, with a predominance on the left side. They can be functional or non-functional, depending on their association with hypercalcemia. The clinical manifestations are various. Some cases of carcinoma arising from parathyroid cysts have been reported suggesting that the surgical removal of all cysts should be strongly considered.

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Hyperparathyroidism Jaw Tumour Syndrome in Pregnancy: A rare coexistence

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Introduction
Only <1% of cases of primary hyperparathyroidism (PHPT) occur during pregnancy. PHPT increases risk of complications such as miscarriage, premature birth and life-threatening maternal hypercalcemic crises. Hyperparathyroidism Jaw Tumor Syndrome (HPT-JT) is a rare inherited cause of PHPT, resulting from CDC73 gene mutations. There are a few reports described about HPT-JT in pregnancy. Although parathyroidectomy is the definite treatment for PHPT, given the scarce evidence on the management of PHPT in pregnancy, questions regarding its safety arise. Additionally, medical therapies such as bisphosphonates, cinacalcet or calcitonin are not recommended, as there is no proven safety.
Objective
We present the case of a woman with HPT-JT, who became pregnant while awaiting surgical treatment.
Clinical Case
A 19-year-old woman with a history of repeated miscarriages and urolithiasis was referred to an Endocrinology appointment due to hypercalcemia of 12.4 mg/dl (8.8-10.6). The remainder study revealed serum PTH of 950 pg/ml (9-72), phosphataemia of 2.2 mg/dl (2.9-5.0), 25-OH Vitamin D of 27 ng/ml (30-100) and normal urinary clearance calcium/creatinine ratio. Cervical ultrasound showed a right inferior parathyroid adenoma. The genetic study identified a CDC73 gene pathogenic variant, confirming the diagnosis of HPT-JT. The clinical situation was explained to the patient, namely the risks associated with pregnancy. Despite this, while awaiting surgical treatment, a 5-week pregnancy was diagnosed, in the context of an episode of abdominal pain. In this patient, we opted for close surveillance and conservative treatment with increased oral hydration and restriction of calcium in the diet, delaying surgery to the postpartum period. Pregnancy complications included: an episode of acute renal colic pain at week 10 of pregnancy, which was treated conservatively; a threatened preterm labor at week 28, that responded positively to bed rest. During pregnancy, calcemia values between 12.7-13.2 mg/dl and PTH between 678-882 pg/ml. Spontaneous vaginal delivery occurred at 39 weeks and 3 days, with a birth weight of 2920g. There were no evident changes in fetal development. Our patient currently awaits postpartum reassessment.
Conclusions
The fact that the patient had become pregnant prior to surgical treatment raised major approach challenges, given the rarity of the clinical situation, the risk of maternal-fetal adverse effects and the scarcity of therapeutic options in pregnancy. Although parathyroidectomy constitutes the definitive treatment for PHPT, the type of treatment during pregnancy is complex and must be individualized, taking into account additional factors such as the severity of hypercalcemia and the risk of post-surgical complications.

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EP188

22q11.2 deletion syndrome diagnosed in the context of a seizure in adulthood

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Introduction
The 22q11.2 deletion syndrome or DiGeorge syndrome (DGS) is rare and the diagnosis in adults is uncommon. The phenotype is highly heterogeneous and of variable severity, including hypoparathyroidism and epilepsy.

Case Report
A 26-year-old man was admitted in the emergency room for inaugural tonic-clonic seizure. He had history of cognitive impairment and learning difficulties. Neurologic examination, brain CT and basic analysis were irrelevant. He was started on an anti-epileptic drug. He was followed up in Neurology and Internal Medicine outpatient clinic. Brain MRI was normal. Electroencephalography showed generalized epilepsy. Laboratory tests revealed total Ca^{2+} 5.7 mg/dl [8.9-10.0], P- 5 mg/dl [2.3-4.7], PTH 8.4 pg/ml [15.0-68.3] and 25-OHD 14 ng/ml. He was started on oral calcium and cholecalciferol supplements with no improvement. At the age of 30, he was referred to the Endocrinology clinic. Accompanied by his mother, he had no history of cervical surgery or irradiation, heart disease or recurrent infections. He had dental plaque due to enamel hypoplasia and had had surgery for spastic flat feet. Family history was irrelevant. He had significant difficulty in noticing typical symptoms of hypocalcemia, but he admitted frequent paresthesia and tiredness in lower limbs since childhood. He had slight facial dysmorphia and normal stature. He was hemodynamic stable, and Trousseau's sign was present. He was started on calcitriol and calcium supplements were adjusted. Symptoms improved for the first time and blood tests revealed clear analytical improvement. Anti-epileptic medication was stopped without new seizures. The remaining study showed normal 24-hour urine calcium, intermediate hyperglycemia and autoimmune thyroiditis; morning cortisol, total testosterone and femur radiographs were normal. The suspicion of DGS was confirmed by genetic study. Complementary evaluation documented mild aortic insufficiency, and there was no evidence of kidney or ophthalmologic alterations. Skin lesions were evaluated by Dermatology and psoriasis and generalized candidiasis were diagnosed. During follow-up, due to poor therapeutic adherence, serum calcium levels have been below target. Currently, however, adherence has improved with maternal support (total Ca^{2+} 8.24 mg/dl).
Discussion
We report a case of DGS diagnosed in the context of a seizure in an adult, but with systemic manifestations since childhood in addition to hypoparathyroidism. We highlight the role of Endocrinology in the correct diagnosis and treatment of this complex patient, with control of hypocalcaemia and its complications and guidance for other comorbidities that also require chronic multidisciplinary follow-up.

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Multiple brown tumors mistaken for bone metastases: Bone scintigraphy and 99m-Tc sestamibi imaging findings

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Introduction
Brown tumors or osteitis fibrosa cystica are benign bone tumors complicating uncontrolled primary or secondary hyperparathyroidism. They may behave aggressively and can be destructive. Their osteolytic aspect may be misinterpreted as skeletal metastases.
Methods
A 37-year-old female patient with chronic renal failure on dialysis, presented with pain and swelling of her left knee for 10 days, with no associated trauma. She gave history of tubulo-papillary carcinoma on renal graft, four years after her renal transplantation, treated with transplantectomy since 2015.
Results
X-rays revealed no fracture, but multiple osteolytic lesions were found in the tibias and the right pubic bone. In view of the suspicion of bone metastases, a whole body computed tomography (CT) was performed, revealing renal osteodystrophy as well as multiple osteolytic and mixed lesions within the costal grid, the dorsal spine and the right pubic spine evoking bone metastases. MRI of the knee revealed a lesion of the 1/3 upper left tibia measuring $46 \times 41 \times 76$ mm blowing the cortex, suggestive of brown tumor. Bone scan showed intense, symmetrical and diffuse uptake of the skull, facial bones and mandible. There was increased and diffuse radiotracer uptake in the dorsal spine and several foci of moderately increased uptake within the costal grid and the right pubis. These lesions were previously described on the CT scan however this appearance suggested a metabolic origin. The patient underwent biopsy from the left tibial lesion which showed histiocytic proliferation with large number of osteoclastic giant cells compatible with a brown tumor. The biological workup revealed hyperparathyroidism with elevated parathyroid hormone (PTH) at 1100 pg/ml (reference range; 15-65 pg/ml). ^{99m}Tc- sestamibi scintigraphy was done which localized a left inferior parathyroid adenoma. Radiopharmaceutical uptake was also noted within several brown tumors.
Discussion and Conclusion
Brown tumors are rare skeletal manifestations of hyperparathyroidism. They can be monostotic or rarely polyostotic with preferentially affecting sites such as skull, jaw, phalanges, pelvis, clavicles, femur and ribs. These tumors give a pseudometastatic radiological appearance. Therefore, they should be considered in the differential diagnosis of osteolytic lesions to avoid unnecessary interventions.

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EP190

Denosumab in the treatment of fracturary osteoporosis: the double effect on bone and glycemic metabolism

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Background
Denosumab (Dmab) is a human monoclonal antibody with an anti-reabsorptive bone effect, used in osteoporosis treatment. It is also suggested that Dmab may improve glucose tolerance through the reduction of hepatic insulin resistance. Some studies have suggested that insulin sensitivity and glycemia can influence bone metabolism.
Aims
To evaluate the relationship between bone turnover markers (BTM) and insulin resistance and glycemia in fracturary osteoporotic patients treated with Dmab.
Methods
Retrospective study of a cohort of osteoporotic patients treated with Dmab for at least 6 months. BTM (CTX - serum C-telopeptide of type I collagen, P1NP - serum procollagen type 1 N-terminal propeptide, BALP - bone alkaline phosphatase and osteocalcin), fasting glycemia and insulin were measured at baseline (T0) and after Dmab treatment (T1). Insulin resistance was estimated using homeostasis model assessment of insulin resistance (HOMA-IR) at T0 and T1. Adequate statistical studies were used, statistical significance was considered for $P<0.05$. Results are expressed as mean $\pm$ SD.
Results
Included 18 patients, 15 postmenopausal women and 3 men, with a mean age 75.5 ± 9.1 years old, treated with Dmab for 23.7 ± 10.1 months. It was observed a reduction of BTM levels after Dmab (BTM T0 vs T1 were: CTX 0.35 ± 0.18 vs 0.14 ± 0.13 ng/ml, $P<0.01$; P1NP 43.7 ± 16.0 vs 21.1 ± 9.7 ng/ml, $P<0.01$; BALP 13.9 ± 5.2 vs 8 ± 2.0 µg/l, $P<0.01$; osteocalcin 17.9 ± 6.9 vs 10.0 ± 4.0 ng/ml, $P<0.01$). After Dmab (T0/T1), fasting glycemia ($98.6 \pm 23.6/93.6 \pm 18.5$ mg/dl, $P=0.04$), fasting insulin ($10.8 \pm 5.3/9.4 \pm 4.8$ µU/ml, $P=0.1$) and HOMA-IR ($2.5 \pm 0.5/2.3 \pm 1.4$, $P=0.43$) decreased. There were no associations between HOMA-IR, insulin or glycemia and each BTM at T0 and T1.
Conclusions
In this group of fracturary osteoporotic patients, Dmab reduced significantly BTM and glycemia. These results may suggest that Dmab can be a good option treatment for patients with diabetes and insulin resistance, both known factors contributing to osteoporotic fractures. Studies with more patients can validate these preliminary results.

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EP191

Severe calcific uremic arteriolopathy lessions and acute hypocalcemia after parathyroidectomy for secondary hyperparathyroidism in haemodialysis patients: Case series

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Introduction
Calcific Uremic Arteriolopathy (CUA) is a rare but severe complication of end-stage kidney disease with one year survival rates between 45-55%. Extensive skin ulcers and concomitant painful purpura are the clinical features and diagnosis criteria as defined by Hayashi. Parathyroidectomy treatment for hyperparatiroidism is reserved for patients with inadequate response to calcimimetics, persistent elevated PTH > 800 pg/ml or calciphylaxis and it has been shown to provide

benefits for all-cause mortality in secondary hyperparathyroidism patients.
Method
Case series of five patients (3 females and 2 males) with a mean age of 51 ± 5.3 years old with end stage kidney disease and hemodialysis programme duration of 9.5 ± 2.7 years. Due to persistent high serum iPTH levels was 1400 ± 270 pg/ml after calcimimetics medication, sub -total parathyroidectomy was indicated in all 5 cases. We evaluated calciphylaxis lessions and iPTH dynamic levels for the next 12 months.
Results
CUA with painfull skin ulcers has occurred in 2 cases, the patients aged 46 and 49 years old, males and with a hemodialysis history of 8 respectively 11 years. The iPTH levels before parathyroidectomy were > 1400 pg/ml in both cases, and they had severe post-surgery hypocalcemia 1.48 mmol/l and 1.53 mmol/l with iPTH levels between 120 and 250 pg/ml. The outcome after surgical debridation, antibiotherapy, discontinuation of anti-vitamin K and nutritional support was favorable with complete skin ulcers remission and stable calcium levels of 1.8-2.1 mmol/l.
Conclusions
The calciphylaxis lessions are rare, especially after parathyroidectomy, when calcium levels are lower and iPTH levels are reduced. Guidelines for CUA therapy are currently lacking and these particular cases show that long term evolution of hyperparathyroidism especially with very high levels of PTH need accurate management .Also the associated severe hypocalcemia is an aggravating factor, as correction with calcium supplements may lead to calciphylaxis lesion progression.

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EP192

Features of diagnosis and management of parathyroid cysts

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The retrospective experience of diagnosis and treatment of 18 people with true parathyroid cysts was studied. Clinical features, ultrasound results, laboratory parameters, surgical aids and subsequent dynamics were studied. All patients were women aged 35 to 77 years. Parathyroid cysts had no clinical manifestations, hyperparathyroidism and compression syndrome were absent. All parathyroid cysts were discovered accidentally during an ultrasound examination of the neck. Often the reason for contacting surgeons was a referral to FNAB due to an erroneous diagnosis of thyroid nodules. Ultrasound data showed that all the cysts were located on the neck, two of them fell behind the collarbone. Most of the cysts (14) were located in the projection of the lower third of the thyroid lobes and below the thyroid gland. The cysts were visualized as rounded or oval formations with clear contours, an echogenic capsule, the absence of a solid component and anechoic contents with distal pseudo-amplification of the echo. Ultrasound criteria included cases of reliable location of cysts outside the thyroid gland, as well as a tendency to increase due to one of the diameters. When determining the size of cysts, their diameter ranged from 10 to 120 mm. Elevated levels of PTH and Ca^{++} in the blood were not detected in any patient. In all cases, a crystal clear colorless liquid was obtained using FNAB, which was one of the diagnostic criteria. When determining the level of PTH in the cystic fluid, a very high (more than 1000 pg/ml) concentration of the hormone was observed in all cases. Cystectomy was performed in 4 cases together with thyroid surgery (thyroid adenomas and nodular goiter). In 10 cases (dimensions more than 30 mm (average volume more than 4 ml), sclerotherapy was performed), in 4 cases - aspiration of cystic contents. The results were tracked 3 months and 1 year after the manipulations. Since all parathyroid cysts were functionally inactive, PTH levels after aspiration, sclerotherapy and cystectomy were not determined. The level of Ca^{++} in the blood after aspiration and sclerotherapy was not determined, and after surgery was measured 24 hours after the intervention. According to ultrasound and laboratory tests, a positive result was obtained in all cases. It was concluded that the presented protocol of examination and treatment of patients is optimal, and the choice of treatment method depends on the size and activity of cysts, as well as on the presence of concomitant pathology.

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EP193

Parathyroid carcinoma: A case report

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Introduction
Parathyroid carcinoma is an uncommon cause of primary hyperparathyroidism. It is responsible of 0.4% to 5% of all cases of primary hyperparathyroidism. Parathyroid carcinoma has a high probability of local recurrence, regional node and distant metastasis and the preoperative diagnosis is challenging.
Case presentation
We report a case of a 66-year-old female patient with medical history of hypertension and chronic kidney failure. She was diagnosed with primary hyperparathyroidism and underwent cervicotomy for an ectopic suprasternal and a right paratracheal parathyroid nodule and histopathology confirmed the diagnosis of parathyroid hyperplasia. One year later, she consulted for persistent hyperparathyroidism with malignant hypercalcemia. Sestamibi parathyroid scintigraphy confirmed hyperfunctioning parathyroid tissue in the right thyroid bed and in the mediastinal area. The cervical MRI revealed an ectopic mediastinal nodule of 11.8 mm. Multiple endocrine neoplasia was excluded. The patient underwent surgical removal of the lower right parathyroid and the mediastinal nodule and histological examination of the specimen confirmed the diagnosis of parathyroid carcinoma with clear cell and on-cocytic features. Postoperative calcium and parathyroid blood levels remained high. The presence of pulmonary metastasis was confirmed after practicing a total body scintigraphy and the patient was referred to oncology for chemotherapy.
Conclusion
Parathyroid carcinoma is a rare tumor. The severity of this pathology is due to the severe hypercalcemia aggravating the mortality and to the risk of local recurrence and distant metastases justifying the prolonged monitoring to improve the prognosis of the disease.

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EP194

Completely intra-thyroidal parathyroid adenoma: A rare entity

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Introduction
Intra thyroidal parathyroid adenoma is an uncommon presentation of primary hyperparathyroidism (PHPT). Herein we report such a patient who had recurrent hypercalcemia after a classical parathyroid exploration.
Case presentation
45 year old female, home-maker had a long standing history of weakness, back and lower limb pain, loss of appetite. Preliminary evaluation at secondary care level revealed hypercalcemia (18.3 mg/dl) with high intact parathyroid hormone (iPTH, 1244.0 pg/ml). 99mTc SestaMiBi scan revealed left inferior parathyroid adenoma for which she underwent left inferior parathyroidectomy elsewhere. Post operatively her symptoms of hypercalcemia returned within few weeks and further evaluation revealed high iPTH(251.10 pg/ml) with hypercalcemia (10.4 mg/dl). Repeat MiBi scan revealed suspected parathyroid adenoma in relation to lower pole of left lobe of thyroid suggesting failed surgery. HR-USG neck revealed no parathyroid adenoma in usual locations and a left lobe thyroid nodule which roughly corresponded to the isotopic activity. USG guided FNAC was non contributory. Patient was subjected to re-exploration by a parathyroid surgeon. Left hemi-thyroidectomy was done and the intrathyroidal mass was removed. Pre-operative iPTH of 1988 pg/ml came down to 55.9 pg/ml within 4 hours of surgery. Intra-opeartive imprint smear showed small clusters of tumor cells with normal to moderate cytoplasm and round to oval nuclei. HPE showed a well circumscribed tumour within left lobe of thyroid with an incomplete fibrous capsule surrounded by thyroid tissue without any capsular or vascular invasion. There were polygonal cells with moderate amount of clear cytoplasm and round to oval hyperchromic nuclei and mild anisocytosis. Post-operative hypocalcemia (6.9 mg/dl) was managed with intravenous calcium and magnesium and oral calcitriol. Patient continues to be on oral calcium plus calcitriol supplement at the 7th post operative week of the second surgery.
Discussion
In a large series of > 10,000 parathyroid exploration for PHPT, 1.2% were partially intrathyroidal while only 0.7% were truly intrathyroidal[1]. Most reported cases were typically diagnosed due to persistent disease post-exploration[2].
Conclusion
Intrathyroidal parathyroid adenoma is a rare cause of PHPT and should be considered as a potential cause for a unsuccessful parathyroid exploration.

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EP195

Primary Hyperparathyroidism and colon cancer: Incidental association or causal link?

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Introduction
Hypercalcemia is often observed in patients with cancer, secondary to the production s of parathyroid hormone (PTH)-related peptides. However, the association of primary hyperparathyroidism (pHPT) and colon cancer is rarely reported.
Case
We present the case of a 76 years old female patient, who was operated one year ago of for a low-grade colorectal adenocarcinoma. As part of her routine workup of her disease she underwent a phosphocalcic assessment which showed hypercalcemia at 120 mg/l, hypophosphatemia at 19 mg/l, an elevated PTH above 300 pmol/l and a 24-hour calciuria of 350 mg/day.The parathyroid Sestamibi scan was performed and the findings were suggestive of a left inferior parathyroid focus. The patient underwent a left inferior parathyroidectomy and the anatomopathological examination was in favor of a parathyroid adenoma.
Discussion and Conclusion
Calcium is considered as a potential anticarcinogenic, these findings can be explained by two possible mechanisms. Firstly, it neutralizes the promoter activity of fatty acids and bile acids in colorectal carcinogenesis. Secondly, calcium is believed to reduce crypt cell hyperproliferation so a decreased level of calcium can lead to hyperproliferation of the colorectal mucosa. In primary hyperparathyroidism the increase in PTH activates 1,25(OH)2D and promotes calcium absorption in the intestine. As a result, the level of calcium in the lumen is decreased, which leads to an elevated risk of colorectal cancer.

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EP196

Depot medroxyprogesterone acetate (DMPA)-associated early-onset osteoporotic fracture with ALPL gene mutation: Challenges and Limitations in the era of molecular diagnostics

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Background
Recent advances in next-generation sequencing technology have greatly increased the number of Variants of Uncertain Significance (VUS) encountered in clinical practice. Herein, we present difficulty in diagnostic path and challenges in a premenopausal woman with an unusual fracture history and osteoporosis.
Clinical Case
A 37-year-old Thai woman with no known underlying disease was diagnosed with osteoporosis (a BMD Z-score of -2.6 at femoral neck) after having developed left proximal fracture femur from a slip and fall accident 6 months earlier. The patient came to see us for further treatments of early-onset osteoporosis. Additional history revealed that intramuscular DMPA injection was continuously used for 7 years as a hormonal contraceptive. Initial work-up for secondary osteoporosis at that time showed only low serum TSH level, vitamin D insufficiency (17 ng/ml), slightly elevated plasma iPTH level (70.5 pg/ml) with normal plasma alkaline phosphatase (ALP). The patient was started on a weekly oral bisphosphonate for 4 months before whole exome sequencing to investigate monogenic bone disorders revealed a rare heterozygous variant c.1069C>T (p.Arg357Trp) of the *ALPL* gene which could cause adult-onset hypophosphatasia (HPP). However, this variant was classified as VUS by the ACMG guidelines. Based on the very low allele frequency from gnomAD, the possibility of pathogenicity of this variant could not be excluded. However, additional testing revealed normal plasma pyridoxal 5′-phosphate (an ALP substrate) together with her history of prolonged use of DMPA which could have adverse bone effects from hypoestrogenism and its glucocorticoid effect did not support the diagnosis of HPP. Extended family members testing to determine whether the variant is shared by other unaffected individuals showed the patient inherited this variant from her mother and her brother without history of fracture also carries this variant. As a result, the possibility of HPP had been disregarded. At follow-up 3 months later, she developed avascular necrosis (AVN) of previous screw fixation at left femoral head and total hip arthroplasty was performed uneventfully.
Conclusions
Identification of rare *ALPL* VUS challenges in deciphering the clinical relevance whether this patient has HPP and bisphosphonate should be discontinued. The underrepresentation of non-European ancestry groups in current genomic databases complicates interpretation of their genetic test results. The patient's clinical presentation remains the most important context for interpreting sequencing results. Our case also highlights the fracture risk from long-term use of DMPA which is widely used as progestogen-only contraceptive method in low and middle-income countries.

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EP197

Body mass index as predictor of bone mineral density in postmenopausal women

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Introduction
In order to detect the subjects at risk for osteoporotic fractures, one should actively search for them, primarily in a group of postmenopausal women, considering clinical risk factors. Body mass index (BMI) is a well-known, significant predictor of bone mineral density (BMD) of entire skeleton.
Aim
The aim of this study was to examine relationship between BMI and BMD in a group of postmenopausal women.
Methods
The study involved a group of 100 postmenopausal women, aged 46 to 70 years. (59.08 ± 6.07). All subjects had their body mass and body height measured and BMI calculated. BMD was determined by DXA method (dual energy X-ray absorptiometry) by Lunar Prodigy Advance Unit. BMD was measured at central skeleton (lumbal spine and both hips). According to densitometry finding, the criterion for osteoporosis is T score less than –2.5 SD. BMI values were correlated with total T score values of the lumbal spine and both hips, as well as total T score values of spine and hip.
Results
Results have shown that BMI was normal in 18% subjects, 1st grade obesity was found in 52%, 2nd grade obesity in 23%, 3rd grade obesity in 7% of subjects. Median BMI value was found in 28.27 ± 4.12. Median lumbal spine T score was– 2.19 SD ± 1.25, and hip T score–1.11 SD ± 0.95. A statistically significant positive correlation ($r = 0.01$) was found between BMI and BMD of the hip, whereas between BMI and BMD of lumbal spine there was no statistically significant correlation. There was a statistically significant correlation ($r = 0.01$) between BMD values of lumbal spine and hip.
Conclusion
In postmenopausal women BMI is more important predictor of hip BMD, as compared to spine BMD. BMD of hip is increased with the increase of BMI and height in postmenopausal women due to considerable endocrine function of fat

tissue which produces leptin and other bioactive peptides which have a protective role in bone structure. A lack of correlation between BMI and BMD of spine in postmenopausal women might be due to predominant effect of lack of estrogen and faster bone metabolism in spinal region.

Keywords: Osteoporosis, obesity, menopausal woman

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EP198

Porphyria presenting as osteoporosis

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Introduction

Secondary osteoporosis is defined as bone loss caused or exacerbated by other clinical disorders. Secondary osteoporosis can be due to a wide range of medical disorders, including endocrine disorders and genetic disorders. We are presenting a clinical case which the patient diagnosed as acute intermittent porphyria while being investigated for secondary osteoporosis.

Clinical Case

41-year-old female patient applied with bone and back pain, itchy dark-colored lesion in the abdomen, abdominal pain during menstruation and nonspecific neurological complaints such as numbness in the arms and headache. The patient had anxiety was using sertraline for the treatment. On physical examination, brown spots were seen on the skin in the lower abdominal quadrants. In laboratory examinations, there was no hypogonadism, parathyroid and thyroid functions were normal. In 24-hour urine analysis, uroporphyrin was detected as 96.92 μg/24 h (0-33 μg/24 h). Bone mineral density (BMD) showed a *Z* score of −2.6 for L2 to L4, −2.7 for the femoral neck and -2.6 for total hip. Her FRAX score showed low risk of osteoporotic fracture. Genetic examination was performed for porphyria due to its clinical compatibility ant the patient was a heterozygote for an exon 9 (NM_000190) *HMBS* variant. The patient was evaluated as acute intermittent porphyria with clinical and genetic results. Antiresorptive treatment was not started due to the low risk of fracture. She was followed up with vitamin D and calcium.

Conclusion

In any patient evaluated for osteoporosis, secondary causes may have contributed to the condition. Various causes of osteoporosis, such as mild asymptomatic hyperparathyroidism, celiac disease, metabolic and genetic disorders, may be clinically unclear. Intensive research is particularly needed in all premenopausal women and men with atraumatic fractures or BMD below 1 SD of same-age control subjects. Porphyria should be kept in mind in patients with atypical abdominal pain or atypical neurologic findings.

Table 1 Laboratory findings of the patient

Laboratory test	Patient's values	Reference range
Creatinine (mg/dl)	0.61	<1.2
ALP(U/l)	96	<98
FSH (mIU/ml)	4.7	1.5-12.4
LH (mIU/ml)	12.14	1.7-8.6
Estradiol (ng/dl)	213.3	30-400
TSH (Uu/ml)	1.26	0.27-4.2
FT4 (ng/dl)	1.3	0.89-1.76
PTH (ng/l)	27.5	15-65
25-OH-D(μg/l)	21.84	30-80
Serum calcium (mg/dl)	9.67	8.8-10.6
Serum phosphorus (mg/dl)	2.7	2.6-4.5
AFP (μg/l)	1.78	0-7

FSH: Follicle-Stimulating Hormone; LH: Luteinizing hormone; TSH: Thyroid-stimulating hormone; FT4: Free thyroxine; PTH: Parathyroid hormone; 25-OH-D: 25-hydroxy vitamin D; AFP: alpha-fetoprotein

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EP199

Osteoporosis in a patient with Glycogen Storage Disease Type I

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Glycogen storage disease type 1 is a rare autosomal recessive disorder. Osteoporosis is one of the long term complications. However factors associated with low bone mass has not fully understood. Metabolic derangements that occur with poor control may contribute to bone disease. Low bone mass could be caused by hypogonadtropic hypogonadism, a unique issue identified in GSD. Herein we report a patient with GSD type 1, osteoporosis and hypogonadotropic hypogonadism. A 20 years old man admitted to our outpatient clinic for evaluation of osteoporosis after femur fracture in 2021. He had a history of Glycogen Storage Disease type 1a that is diagnosed in infancy with recurrent hypoglycemia. He is currently managed with Glycosade however he has suboptimal metabolic control. He has multiple hepatic adenomas stable for two years on serial abdominal MR scans. He previously underwent a right lobe partial liver resection for probable hepatocellular carcinoma and pathology showed hepatic adenoma. On physical examination his height was 158 cm and weight was 54 kg. He has tanner 3 pubic hair and stage 4 genitalia. His biochemical tests confirmed hypogonadotropic hypogandism, other pituitary hormones were normal. His BMD at L1-L4 was 0.420 with a *Z* score of -6.0. At age 17 years he was evaluated for low bone mass. According to his medical records he underwent spontaneous puberty however his bone mineral density (BMD) at lomber vertebrae was 0.436 g/cm^2 and Z score -5.3 at that time. Vitamin D replacement was started nevertheless he did not use it regularly. Since there was not evidence for use of conventional osteoporosis treatment in Glycogen storage disease related osteoporosis we intended to treat his hypogonadism first. In 2021 at the age of 19 he was started on transdermal testosteron. After a year with transdermal testosteron his hepatic adenomas were stable in MR imaging. His bone mass ameliorated (L1-L4 BMD 0.648 g/cm^2 and *Z* score -4.7) despite his poor metabolic control. Hypogonadotropic hypogonadism may be an important factor contributing to bone loss in patients with GSD. Testosteron replacement may restore bone mass. GSD type 1 patients are at risk for potential malignant transformation of hepatic adenomas, testosterone therapy should be carefully monitored.

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EP200

Cortisone-induced osteoporosis: A dreaded complication of prolonged corticosteroid therapy

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Introduction

Cortisone-induced osteoporosis (CO) is the most frequent complication of corticosteroid therapy. It is the first cause of secondary osteoporosis. The aim of this study is to clarify the characteristics of CO.

Patients and Methods

We report a retrospective study of 39 cases of CO among 128 cases of osteoporosis during a 15-year period. The diagnosis of CO was based on a bone densitometry (BMD) of more than -1.5 standard deviations.

Results

Thirty-nine cases of CO were collected. Its frequency is 30.5% of the total osteoporosis series and 85.7% of secondary osteoporosis. There were 34 women (87.5%) and 5 men (12.5%). The average age at diagnosis was 59 years. CO was more frequent in younger subjects with a significant correlation ($P=0.011$). All our patients received long-term systemic corticosteroid treatment. The average cumulative dose of corticosteroid therapy (CT) was 26 g of prednisone (extremes 0.4-65 g). The average duration of CT was 14.5 years (extremes 2-18 years). The indications for CT were: systemic disease in 33 cases, haematological disease (3 cases), dermatological disease (2 cases) and uveitis (1 case). BMD showed a mean vertebral T-score of -2.78 standard deviations. In addition to vitamin and calcium therapy in all patients, bisphosphanates were administered in 23 patients and strontium ranelate in one case.

Conclusion

CO is the main cause of secondary osteoporosis in our series.

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EP201

A Late Diagnosed Neurofibromatosis Case During Preoperative Evaluation For Scoliosis

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Objective
Neurofibromatosis type 1 is an autosomal dominant inherited neurocutaneous condition characterized with multipl cafe-au-lait spots, neurofibromas, predisposition to malignancies, and the incidence of disease is 1:3000. Patients are diagnosed according to diagnostic criteria and 97% of the patents meet the criteria before 8 years of old. Diagnosis and follow-up of patients for manifestations of neurofibromatosis is important for early diagnosis and treatment of malignancies.
Case
Twenty-one year old female patient admitted to neurosurgery outpatient clinic with complaint of scoliosis. She was consultated to endocrinology clinic for low bone mineral density levels and osteoporotic findings in vertebral x-ray examination. In physical examination she was short statured and she had growth retardation. She had multipl cafe-au-lait spots and scoliosis. On right lower limb, she had a brown lesion and after consultation with dermatology clinic it was considered as plexiform neurofibroma. Her bone mineral density level (BMD) in L1-L4 was 1.006, z score was -0.7, femur neck BMD was 0.669 z score was -2.1. Her osteocalcin level was 21.5 ng/ml (9-42), c-telopeptide was 0.23. Hypophysial hormones were evaluated and her IGF-1 level was found to be low according to age reference range. Insulin tolerance test was performed and her growth hormone was found to be 0.206 when her blood glucose was 36 mg/dl. In family history, her mother and brother were also learnt to have multiple cafe-au-lait spots and in physical examination her mother had cutaneous neurofibromas. Neurofibromatosis diagnosis was confirmed after genetic consultation and genetic test. Hamartomatous lesion in both basal ganglia and thalamus and in right frontal lobe were found in cranial magnetic resonaunce imaging (MRI). In abdominal MRI, neurofibromas in right coxofemoral articulation and right acetabulum were found. Her urine metabolites were examined for pheochromacytoma and found in normal levels. Follow-up visits were planned and she was concultated to relevant departments. Her mother and brother were also diagnosed as neurofibromatosis.
Discussion and Conclusion
Patients with neurfibromatosis have a high predisposition to develop both benign and malign tumours. Although most of the manifestations effect the nervous system, multiple organs and tissues can be affected. Patients can present with different clinical symptoms to different clinics so being aware of the different clinical manifestations of the disease is important for prompt diagnosis.

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EP202

Gayet Wernicke's encephalopathy: An exceptional complication of primary hyperparathyroidism

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Introduction
Gayet Wernicke's encephalopathy (GWE) is a severe encephalopathy secondary to acute thiamine (vitamin B1) deficiency which may lead to severe sequelae or death if the diagnosis is delayed. We report the first case in the literature of an association between GWE and primary hyperparathyroidism (PHP) in a man.
Observation
He was a 57 years old man, with a personal history of hypertension and primary infertility, who presented with incoercible vomiting, asthenia and fever. Biological finding revealed hypokalaemia (2.7 mmol/l), renal failure (creatinine clearance = 29 ml/min), hypophosphaemia (0.45 mmol/l), hypercalcaemia (4.02 mmol/l) with electrical findings on the elctrocardiogram (QT shortening) requiring an emergency haemodialysis session. PHP was diagnosed with a serum parathyroid hormone (PTH) level of 570 pg/ml (8.7 times upper limit of the range). Cervical ultrasound showed a plunging cystic mass with some parietal calcifications, measuring 40 × 56 × 90 mm and largely necrotic. Parathyroid MIBI scan showed fixation in the periphery of the mass. Parathyroid carcinoma is the most likely diagnosis. The evolution was marked by the appearance of epileptic seizures, followed by an alteration in his state of consciousness. Cerebral MRI showed bilateral and symmetrical signal abnormalities of the mamillary, hypothalamic, medial thalamic bodies and the periaqueductal white matter and around the third and the fourth ventricule (V3 and V4) in FLAIR hypersignal, moderate Diffusion hypersignal in accordance with an EGW. The patient was treated with intraveinous thiamine followed by oral thiamine 100 mg once daily as maintenance dose with favourable outcome.
Conclusion
Although EGW is a known complication of alcoholism, it should be noted that it can occur regardless of this addiction so as to avoid delaying the diagnosis of a curable cause of hypercalcaemia.

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EP203

Multiple Endocrine Neoplasia type 1: A case report

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Introduction
Wermer syndrome or multiple endocrine neoplasia type 1 (MEN1) is a rare hereditary disease characterized by the presence of generally benign tumors of the endocrine glands.
Observation
We report the case of a 68-year-old patient with a family history of a sister having a primary hyperaldosteronism and a personal history of primary hyperaldosteronism who was referred to our department for the exploration of asymptomatic hypercalcemia. The biological assessment showed an hypercalcemia at 2.96 mmol/l, an hypophosphoremia at 0.71 mmol/l and a high PTH at 220 pg/ml with a normal creatinine level at 83 µmol/l and a normal vitamin D level at 43 ng/ml in favor of the diagnosis of primary hyperparathyroidism. Cervical ultrasound showed a left upper parathyroid nodule of 1.5 x 1 cm but which had no scintigraphic correspondence. The cervico-thoracic scanner showed a double localization of ectopic parathyroid adenoma. The association of primary hyperaldosteronism with primary hyperparathyroidism falls within the scope of MEN1. Therefore, the patient benefited from a subtotal parathyroidectomy given the significant risk of recurrence.
Discussion
The particularity of our case is that MEN1 was revealed at an advanced age by the association of primary hyperaldosteronism with primary hyperparathyroidism. Hence the need to always be vigilant in front of any endocrine neoplasia. In addition to early diagnosis, multidisciplinary care and follow-up are mandatory and for life.

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EP204

Atypical parathyroid adenomas, a challenging diagnosis and management - Case Report

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Introduction
Primary hyperparathyroidism is typically caused by a parathyroid adenoma (80-85% of the cases). Very rare causes are represented by parathyroid carcinoma and atypical parathyroid adenoma (0.5-1.5% of the cases). Atypical parathyroid adenomas have atypical histological features, not sufficient to be considered a carcinoma, and have an uncertain malignant potential and risk of recurrence. We report the case of a 66-year-old man referred from another medical center for severe hypercalcemia (14.41 mg/dl) with normal serum phosphate (3.24 mg/dl) and elevated PTH (1376 pg/ml - 20 fold of the normal level). The patient mentioned bilateral gonalgia and bone pain for 5 years. His personal history revealed permanent atrial fibrillation, class II congestive hearth failure and bilateral nephrolitiasis. Laboratory evaluation showed a highly elevated serum calcium (13.7 mg/dl), and PTH (1128 pg/ml) with normal serum vitamin D level, confirming the diagnosis of primary hyperparathyroidism. Screening for multiple endocrine neoplasia was negative. The cervical ultrasound revealed the presence

of a 4.13/2.27 cm hypoechoic image, posterior to the left thyroid lobe, which deviated the trachea, suggestive of a left inferior parathyroid adenoma. Cervical CT scan revealed a 2.6/3.5/5.7 cm nodular heterodense process in contact with the left thyroid lobe. T scores of right femur (-1.1 SD) and distal radius (-1.3 SD) on osteodensitometry showed osteopenia. The patient received intravenous furosemide and bisphosphonate therapy to control the hypercalcemia before he was referred to the surgery department for left inferior parathyroidectomy. After surgery PTH levels dropped significantly (24.83 pg/ml), but 4 months after surgery PTH levels increased (387.5 pg/ml) with normal calcium level (8.9 mg/dl). Histopathological exam concluded to atypical features of the adenoma that were suggestive but not diagnostic of parathyroid carcinoma.
Conclusion
The diagnosis and management of the atypical adenoma is still challenging because there are no specific guidelines for the follow-up of patients after parathyroid surgery. Although low, there is a risk of recurrence that can occur many years after initial presentation, so long-term yearly monitoring of calcium concentrations after the surgery is recommended. Once the histopathological diagnosis has been confirmed, studies suggest that immunohistochemistry may be a good approach in differentiating between benign and malignant parathyroid masses.

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EP205

Hypercalcaemia as the first manifestation of lymph node tuberculosis

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Introduction
Tuberculosis is a granulomatosis with systemic manifestations. Pulmonary involvement is usually in the foreground. Rarely, hypercalcaemia initiates the pathology. The incidence of hypercalcaemia in tuberculosis varies according to studies and regions between 2 and 25%, with the highest incidences in the most isolated countries and those with the highest calcium and vitamin D intakes.
Clinical Case
This is the case of our patient known for basedow's disease treated by iratherapy; 3 years after stabilization of her hyperthyroidism she presents a frank hypercalcemia. The hormonal exploration is in favour of an extra parathyroid hypercalcaemia. Cervical ultrasound revealed a granulomatous left supra-clavicular adenopathy which was punctured in favour of lymph node tuberculosis. 3 months after the start of anti-tuberculosis treatment, the blood calcium level was normalized.
Conclusion
In tuberculosis, hypercalcaemia is due to extrarenal synthesis of 1,25(OH)2-vitamin D3 by granuloma macrophages with 1-alpha hydroxylase activity. Within the granulomas, the binding of 1,25(OH)2-vitamin D3 to its specific receptors modulates the immune response and decreases the inflammatory response that causes tissue damage.

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EP206

Severe PTH-dependent Hypercalcemia Secondary to Atypical Parathyroid Adenoma

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Introduction
Hypercalcemia is not uncommon in clinical practice and may present as a life-threatening emergency. Its main aetiologies are primary hyperparathyroidism (80% parathyroid adenomas; 20% multiglandular hyperplasia, $<1\%$ parathyroid carcinomas) and hypercalcemia of malignancy, with or without presence of bone metastases.
Case Report
We present a case of a 77 years-old male, submitted to a subtotal gastrectomy at the age of 73 due to a perforated duodenal ulcer and a partial right nephrectomy due to clear cell renal carcinoma limited to the kidney at the age of 74, under annual surveillance. Admitted for severe hypercalcemia associated with acute chronic low back pain in the last two months, gait imbalance, loss of strength in the lower limbs, anorexia, weight loss of 3 kg, polyuria and polydipsia. He was dehydrated, with temporal-spatial disorientation and confusion. Cranial-CT was normal, and EMG showed an axonal sensory-motor peripheral polyneuropathy with sensory predominance. His blood tests revealed PTH 1392 pg/ml, ionized calcium 2.29 mmol/l, total calcium 4.06 mmol/l phosphorus 0.81 mmol/l, vitamin D 20 nmol/l, alkaline phosphatase 193 U/l, Creatinine 1.78 mg/dl. Cervical ultrasound suggested a parathyroid adenoma and TC-99 Sestamibi scintigraphy corroborated parathyroid adenoma/hyperfunctioning left upper parathyroid tissue. Abdominal / pelvic CT excluded renal lithiasis and local recurrence of the renal neoplasm, however exposed focal lytic lacunar lesions in the lumbar vertebral, the largest in L3, suggestive of lytic metastasis and signs of bone demineralization. Bone biopsy of the vertebral lesion showed marked hypocellularity, edema and fibrosis, without osteoclasts or malignant cells. Protein electrophoresis and urinary immunofixation was not suggestive of monoclonal gammopathy. He underwent surgical excision of the parathyroid with $2.6\times1.5\times1$ cm and pre-op PTH 661.0 pg/ml and at 15 min 130.0 pg/ml whose anatomopathology confirms a non-capsulated parathyroid gland or only partially covered by a thin capsule, consisting of proliferation of principal cells without cytological atypia, rare figures of mitosis and necrosis, and with no images of vascular or perineural invasion.
Discussion
Despite considering the hypotheses of tumour hypercalcemia due to PTHrP or secondary to osteolytic metastases, PTH values do not favour them. The case raises the possibility of an Atypical Parathyroid Adenoma. Only long-term follow-up with surveillance of local recurrence and distant metastases will allow a correct diagnosis.

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EP207

Primary hyperparathyroidism revealed by multiple brown tumors: A case report

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Introduction
Primary hyperparathyroidism revealed by multiple brown tumors is rare. We report the case of a patient with primary hyperparathyroidism on parathyroid adenoma discovered in front of multiple brown tumors.
Case Presentation
A 72-year-old female patient, who presented for 6 months a functional impotence of both lower limbs with paraparesis, associated with bone pain from where the realization of a phospho-calcium assessment returning in favor of an hyperparathyroidism. The diagnosis of localization confirmed the presence of a parathyroid adenoma. It also showed the presence of bone masses at the level of the scapulae, right clavicle, at the level of the costal, dorsal vertebrae with a medullar compression. A bone biopsy was performed showing an aspect in favor of multiple brown tumors. The patient underwent a medullary decompression surgery as well as a parathyroid surgery after normalization of the phospho-calcium balance. The postoperative course was simple with a good evolution.
Discussion and Conclusion
A brown tumor is a benign bone lesion caused by localized and rapid osteoclastic turnover resulting from hyperparathyroidism. Hyperparathyroidism revealed by multiple brown tumors is rare, few cases are reported in the literature and they are rarely described in the axial skeleton as in our patient's case. Its diagnosis is often difficult in the presence of polyostotic lytic lesions with hypercalcemia mimicking bone metastases. Bone manifestations are rarely revealing of the disease since they are present only at a late stage and are seen in only 2% of cases.

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EP208

Post-surgical hypoparathyroidism with teriparatide treatment

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Post-surgical hypoparathyroidism occurs as inadvertent removal or irreversible damageparathyroid disease, irreversible or permanent causing decreased action of parathormone leading to hypocalcemia and hypophosphatemia.
Clinical Case
A 52-year-old woman referred from our outpatient clinics due to severe hypocalcemia symptomatic; hand and foot cramps, and hyperphosphatemia:

albumincorrected calcium. (5.52 mg/dl and phosphate of 6.6 mg/dl). She presents a history of total thyroidectomy in 2021 due to Grave's disease with severe exophthalmos, which therefore performed a post-surgical hypoparathyroidism. During successive revisions in queries, it persists hypocalcemia despite increasing the dose of your usual treatment: calcium carbonate 6 tablets/day, levothyroxine 100 mg every 24 hours, Calcitriol 0.5 mg 3 tablets daily day, Vitamin D 25000ui monthly. Admission for intravenous calcium replacement was decided, in addition to oral contributions of the same and calcitriol. Dose reduction of intravenous calcium was attempted multiple times to achieve its complete withdrawal but returned to symptomatic hypocalcemia. During admission, a study was started to rule out causes of calcium absorptive deficit, discarding it and modifying the calcium formula to calcium pidolate for a better absorption. A nephrological study was performed to rule out causes of excessive losses due to urine that would justify the poor response to treatment, without detecting kidney disease chronicle. Given the therapeutic failure, other therapeutic alternatives were reviewed, deciding start treatment with Teriparatide (rH-PTH) 20 mg every 24 hours, assessing various satisfactory clinical studies, and proceeding in accordance with the literature and with the consent of the patient to start treatment without specific indication. It was obtained satisfactory response with decreased phosphate levels and elevated calcium in blood; Laboratory tests on discharge: calcium corrected for total protein 8.24, phosphate 3.5, allowing withdrawal of intravenous calcium gluconate and allowing home discharge with this outpatient treatment: Teriparatide 20 mg every 24 hours, Calcitriol 0.5 mg every 12 hours, calcium pidolate 1 over every 8 hours, levothyroxine 100 mg every 24 hours. In the following check-ups, the patient has maintained calcium and phosphate levels within range without any symptoms, maintaining the same treatment with Teriparatide 20 mg every 24 hours.
Conclusions
PTH replacement therapy with rh,,PTH regulated mineral homeostasis of calcium and phosphate metabolism towards normality in this patient.

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EP209

Hungry bone syndrome after Graves' disease surgery in children

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Although rare in children, Graves' disease remains the major cause of hyperthyroidism. Positive diagnosis is easy, but management can be extremely problematic.
Case Report
We report the case of a 13 year old female patient treated for Graves' disease since 4 years; non compliant to treatment; after adjustment of therapy and achievement of euthyroidism; a surgical cure is programmed. 24 hours after surgery, severe hypocalcaemia appeared, requiring parenteral treatment with injectable calcium for 1 month. The elements in favour of hyngry bone are a non-elevated phosphorus as well as osteopenia on bone densitometry. After 1 month of treatment with injectable calcium associated with oral calcium substitution and 1 alphacalcidal; the phosphocalcic balance improves and the treatment with injectable calcium is stopped.
Discussion
Hyperthyroidism in children is characterized by an increase in bone resorption which is reversed after total thyroidectomy where resorption decreases and bone absorption increases leading to bone hungry syndrome and severe hypocalcaemia. For this reason, it is important to assess bone damage by BMD prior to thyroidectomy to predict the risk of hungry bone syndrome and ensure adequate management

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EP210

Primary hyperparathyroidism and papillary thyroid carcinoma: Incidental association or causal link?

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Introduction
Primary hyperparathyroidism is a frequent pathology, its association with papillary thyroid carcinoma is rare.
Case Report
A 53 year old patient was admitted for management of primary hyperparathyroidism. The biological work-up showed a blood calcium level of 120 mg/l, parathyroid hormone (PTH) 4 times the normal range and hypophosphatemia. Cervical ultrasound showed a right parathyroid nodule with thyroid nodules classified Tirads 4, MIBI scintigraphy had objectified 2 right upper and lower parathyroid adenomas. The patient benefited from a right parathyroidectomy with isthmolobectomy, the anatomopathological study concluded to a parathyroid adenoma with main cells associated with a papillary carcinoma of the thyroid.
Discussion
The association between primary hyperparathyroidism and papillary thyroid carcinoma has been reported in 2.4-4.3% of patients with primary hyperparathyroidism. For some, this association could be explained by the embryological origin and shared genes. This observation illustrates the interest of the "check up" of the thyroid before any parathyroid surgery for a better management.
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EP211

Parathyroid gland locations during surgery

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Introduction
Typically, there are 4 parathyroid glands in humans: 2 superior parathyroid glands usually located near the crico-thyroid joint, and 2 inferior parathyroid glands near the inferior pole of the thyroid gland. However they can be variable in number and location. Awareness of their potential location is crucial for the operating surgeon.
Objective
The purpose of this study is to describe parathyroid gland locations found during surgery.
Material and Methods
A retrospective study including 81 cases of hyperparathyroidism, operated between 2001 and 2021.
Results
The mean age was 53.2 years. Our study included 67 cases of secondary hyperparathyroidism and 14 cases of primary hyperparathyroidism. All patients, having secondary hyperparathyroidism, underwent subtotal 7/8 parathyroidectomy. In the majority of cases (80.6%), the parathyroid glands were found in their usual locations, without intraoperative challenges. Intrathymic localization was noted in 5 cases (thymectomy was performed in these cases). Two parathyroid glands were superposed in 5 cases. Parathyroid glands were located in the recurrent laryngeal nerve's entry point into the larynx, in 3 cases. In cases of primary hyperparathyroidism, intraoperative difficulties were noted in 4 cases: prevertebral parathyroid gland (1 case), latero-tracheal parathyroid gland (2 cases) and parathyroid gland located between the trachea and the esophagus (1 case).
Conclusion
A knowledge of the unusual anatomic locations of parathyroid glands is crucial to operative success during parathyroid surgical exploration. Preoperative imaging can also helpful in the guidance of the surgical procedure.

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EP212

Severe proximal myopathy revealed a primary hyperparathyroidism: about a case and literature review

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Introduction
Proximal myopathy presents as symmetrical weakness of proximal upper and/or lower limbs. There is a broad range of underlying causes including drugs, alcohol, endocrine and metabolic myopathies such as primary hyperparathyroidism.
Observation
We describe a 48-year-old male, hospitalised in neurology departement for exploration of severe proximal myopathy. Cliniquely, he presented progressive debilitating muscle weakness, severe muscle wasting and recurrent muscle spasms over 6 months. He also had bone pain, anorexia and weight loss. He had a

symmetrical proximal myopathy and muscle wasting marked in upper limbs. Biological explorations found a hight level of calcium 3.12 mmol/, hypophosphoremia 0.71 mmol/l, PTH 175 pg/ml, hight 24-hour urine calcium 851 mg/j, wich is suggestive of primary hyperparathyroidism. The creatine kinase (CK) levels was elevated of 637 U/l (30-200). Parathyroid ultrasound and SESTAMIBI scintigraphy localised a hyperfunctioning right inferior parathyroid adenoma of 16 mm. The levels of PTH inside the adenoma was 4070 pg/ml. Bone mineral density indicate an osteopenia (low bone density). He underwent successful parathyroidectomy following treatment with hyperhydration and intravenous pamidronate . There was resolution of muscular spasms, weight gain and normalisation of his calcium, PTH and and CK levels. The histopathological examination confirmed the parathyroid adenoma.

Conclusion

Severe proximal myopathy is a rare complication of primary hyperparathyroidism. Prompt diagnosis and parathyroidectomy can prevent complications and improve clinical outcomes.

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EP213

Autoimmune hypocalciuric hypercalcaemia: A diagnostic dilemma

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Introduction

Hypercalcaemia is a relatively common medical condition affecting around 1% of the general population. Around 90% of the cases are due to either primary hyperparathyroidism (PHPT) or malignancy. Familial hypocalciuric hypercalcaemia (fHH) is a rare autosomal dominant condition that can result in hypercalcaemia. It has an estimated prevalence of1 in 78 000. In most of the cases, fHH is due to a mutation in the calcium-sensing receptor gene (CaSR). Other rare cases of fHH (fHH2 and fHH3) are due to mutations in the GNA11 gene and AP2S1 gene respectively. Very rarely, it can be caused by autoantibodies directed against the CaSR. Differentiating between fHH and PHPT can be difficult in the absence of family history. Normal PTH levels and low Calcium/Creatinine clearance ratio (< 0.01) are in favour of fHH. Resection of the parathyroid tissue might not lead to normalisation of the serum calcium level in fHH. Therefore, reaching an accurate diagnosis is crucial. Herein, we present a patient with hypercalcemia, normal PTH and low urinary Ca:Cr clearance ratio (UCCCR) in the absence of family history and with normal genetic testing. The presence of autoimmune hypocalciuric hypercalcaemia (AHH) was therefore suspected and confirmed. Due to the rarity of the condition, only a few cases have been reported.

Case Report

A 49-year-old lady was referred to the endocrinologist with hypercalcaemia and normal parathyroid hormone. She was symptomatic with fatigue and tiredness. She had a history of kidney stones. Her DEXA scan showed mild degree of osteopaenia. She was thoroughly investigated locally. Her tests showed very low UCCCR (<0.001) on 3 occasions and low 24-hour urinary calcium. An ultrasound scan and SESTAMIBI scan failed to localise any parathyroid abnormality. Genetic testing was negative for CaSR, GNA11 or AP2S1 gene defects. She was considered for exploratory surgery as possible PHPT. She was then referred to us for a second opinion. A repeat urine calcium was very low and she was found to suffer from mild autoimmune hypothyroidism. This raised the possibility of AHH. Anti-parathyroid antibodies were found to be positive. The patient was started on Cinecalcet which has helped reducing her calcium level and improving her symptoms.

Conclusion

This case demonstrates the diagnostic dilemma in hypercalcaemia that may lead a patient to undergo unnecessary invasive surgery. AHH should be suspected in patients with no clear surgical target and low urine CCCR if the genetic testing is negative.

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EP214

The difficult diagnostic of cystic adenomas of the parathyroid gland

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Context

Cystic adenomas of the parathyroid gland are relatively rare, with an estimated incidence of 0.3-1.5% of all parathyroid tumors. These tumors are benign and typically present as a single cyst or multiple small cysts within a solid nodule. Due to their rarity and nonspecific imaging features it may be challenging to diagnose preoperatively. However, the diagnosis is confirmed by fine-needle aspiration (FNA) biopsy and pathological examination of the tissue obtained by FNA.

Case Illiustration

We report the case of a 69-year-old woman admitted to endocrinologist's due to increased sweating and worsening eyesight. The patient had a multifocal goitre that did not require any particular treatment. She was found to have hypercalcemia (2.95 mmol/l; normal: 2.2-2.65 mmol/l), hypercalciuria (10.03 mmol/24 h; normal 0-6.2 mmol/24 h) and elevated PTH (26.4 pmol/l; normal: 1.26-6.74 pmol/l). The plasma phosphorus (0.86 mmol/l; normal: 0.81-1.45 mmol/l), urine phosphorus (30.0 mmol/24 h; normal: 12.9-42 mmol/24 h) and 25-hydroxyvitamin D (76.60 nmol/l; normal: 70-250 nmol/l) were normal. There was no renal failure or osteoporosis. Ultrasonography of the neck revealed a $1.4\times 0.7\times 0.9$ cm cystic mass below the left lobe of the thyroid gland. The nodule found in ectopic thyroid tissue had a mixture of solid and cystic components, this is not a typical feature of a parathyroid gland. SPEC/CT of the neck and mediastinum with 99mTc-MIBI was performed. There was no evidence of accumulation of radiopharmaceutical 99mTc-MIBI, the absence of a parathyroid adenoma was confirmed. As a result of the high previous suspicion of the parathyroid adenoma, it was decided to conduct a fine-needle aspiration of the solid nodule. Cytological and biochemical tests (PTH analysis in rinse material revealed high PTH (210.6 pmol/l)) confirmed parathyroid gland. The multidisciplinary consortium made the decision that surgical treatment is the most appropriate treatment for a parathyroid adenoma. After a parathyroidectomy, histological examination was performed, the diagnosis of a cystic parathyroid adenoma was confirmed. Additionally, post-operative laboratory tests showed normal levels of calcium (2.44 mmol/l) and PTH (2.03 pmol/l) which indicates that surgery was successful.

Discussion

Cystic parathyroid adenomas are rare and have unique characteristics that can make them challenging to diagnose and treat. An experienced endocrine surgeon and multidisciplinary team approach is recommended to manage these cases.

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EP215

Short-term treatment with 2000IU of cholecalciferol in patients with secondary hyperparathyroidism due to vitamin d insufficiency

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Introduction

Conventional treatment of secondary hyperparathyroidism (SHP) requires supplementation of vitamin d analogues combined with calcium however several studies have reported concerns regarding the safety of calcium supplements particularly in the long term. If vitamin d without concomitant calcium supplementation is sufficient to prompt a fall in the parathyroid hormone (PTH) is still not known with certainty. The purpose of our study was to investigate if vitamin d without calcium effectively suppresses PTH secretion in patients with vitamin d deficiency and a history of gastrointestinal complication in calcium preparations.

Materials and Methods

29 healthy individuals with SHP due to vitamin d insufficiency were enrolled. Treatment with calcium carbonate and vitamin d suggested to all patients while in those with a history of previous side effects due to calcium intake vitamin d only recommended. Group A ($n=16$) received 2000 IU vitamin D (Cholecalciferol), and Group B ($n=13$) received 600 mg calcium carbonate, together with 2000 IU vitamin D, for 60 days. Demographic and laboratory characteristics (serum levels of 25(OH)D, calcium, phosphorous, creatinine, albumin and intact PTH (iPTH) were evaluated at baseline and at the end of the study.

Results

Treatment significantly reduced iPTH and increased 25(OH)D levels in both groups. In vitamin d alone group a significantly increase of phosphorous levels observed. No other significant difference was detected between the two groups.

Conclusion
These preliminary data indicate that 2000IU of daily vitamin d constitute a sufficient alternative and could be preferred particularly when calcium intake may lead to unfavorable side effects or is contradicted.

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EP216

Brown tumor revealing primary hyperparathyroidism

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Introduction
Hyperparathyroidism is a frequent endocrinopathy, often diagnosed in the stage of asymptomatic hypercalcemia. The revelation by a bone or renal complication has become increasingly rare dominated by osteoporosis and brown tumors giving a blown aspect of the cortices exposing to pathological fractures. We report 2 cases of primary hyperparathyroidism revealed by a brown tumor and pathological fracture.
Observation 1
This is a 52 year old female patient, followed up for bilateral renal lithiasis for 20 years, admitted for etiological assessment of bone lesions of the pelvic girdle discovered incidentally on a uroscanner, without polyarthralgias, without polyuropolydipsic syndrome nor constipation nor nausea nor vomiting nor fever. The diagnosis of a primary hyperparathyroidism was retained in front of a corrected hypercalcemia to 119 mg/l a hyperparathormonemia to 1200 ng/l and a normal phosphatemia to 25.34 ng/ml, a calciuria of 24 h raised to 268 mg/24 h with localization of a parathyroid adenoma to the ultrasound. Parathyroid scintigraphy with Sestamibi not done due to the patient's lack of financial means.
Observation 2
The patient was 66 years old, without any pathological history, admitted for exploration of a primary hyperparathyroidism revealed by a fracture of the femoral diaphysis on a pathological bone whose anatomopathological examination was in favor of a brown tumor. The biological work-up revealed a corrected hypercalcemia at 140 mg/l, a hyperparathomemia at 1936 ng/ml, a hypophosphatemia at 23.17 mg/l, a 24-hour high calciuria at 246 mg/24 h, and on ultrasound and cervico-thoracic CT scan a parathyroid adenoma of 2.7 cm confirmed by the histological study. The evolution was marked by the installation of the hungry bone syndrome with a good evolution under calcium supplementation.
Conclusion
Brown tumors represent a rare and not exceptional bone complication to be evoked in front of each lytic giant cell lesion and requiring the search for primary hyperparathyroidism given the insidious character of this endocrinopathy while eliminating an underlying malignant process.

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EP217

Hypocalcemia in a term neonate of a mother with gestational diabetes: A case report

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Introduction
Maternal diabetes is described as a risk factor for neonatal hypocalcemia along with maternal vitamin D deficiency or maternal hyperparathyroidism. The frequency of hypocalcemia in a diabetic mother is 20 and 60%, but low in gestational diabetes (GD).
Observation
A 38 year old female patient, with a pregnancy estimated of 35 weeks of gestation, was referred to our department for the management of her gestational diabetes, her cycle was very unbalanced, and her general check-up was without any particularity, especially her phosphocalcic balance. The patient was put on insulin therapy with good evolution, 2 Weeks later; the patient gave birth to a girl with neonatal hypocalcemia.
Discussion and Conclusion
Diabetes is a pathology with fetal and neonatal risk of varying severity .The mechanism of occurrence of neonatal hypocalcemia, its pathophysiology is still unknown today. Studies have established a link between the risk of hypocalcemia in the neonatal period and the maternal glycemic control observed during pregnancy. There is an association between the degree of severity of diabetes and the blood glucose level at birth. The prognosis is better in the case of GDM, especially if it has remained balanced throughout the pregnancy.

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EP218

Hypercalcemia and confusional syndrome: A case report

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Introduction
Severe hypercalcemia is an uncommon but potentially life-threatening condition. Calcium plays a variety of roles and explains the impact of hypercalcemia on the functioning of different organs. We report the case of a patient with severe hypercalcemia revealed by a confusional syndrome.
Observation
A 60 year old male patient, with a medical history of hypertension under treatment, presented a confusional syndrome of progressive onset which worsened towards agitation and disturbance of consciousness hence his admission to the emergency room. The biological assessment was in favor of hypercalcemia at 210 mg/l, a functional renal insufficiency and hyperparathonemia at 2217 pg/ml (33 × the normal range). The patient benefited from rehydration associated with 2 sessions of dialysis due to agitation and worsening of his symptomatology, as well as specific treatments, inhibiting bone resorption. Unfortunately the evolution was marked by the death of the patient.
Discussion and Conclusion
Hypercalcemia is a life-threatening emergency with potentially fatal cardiac, neurological and renal complications. The treatment of acute hypercalcemia will be undertaken in the intensive care unit and includes general measures such as rehydration and diuresis training by diuretics as well as specific treatments, inhibiting bone resorption, biphosphonates associated initially or not with calcitonin.

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EP219

Super bone scan: metabolic or secondary origin: Discussion around a clinical case

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Introduction
– The "super bone scan" is a peculiar condition characterized by extremely high bone uptake compared to soft tissue, with no visualization of renal radioactivity.
– Super bone scan has been described in relation to several conditions such as metastatic disease (prostate/breast cancer), metabolic bone disease (Paget's disease/hyperparathyroidism) and myeloproliferative disorders.
Clinical Case
– A 75 year old man, having as ATCD: a HTA under treatment.
– For one year, he has been suffering from diffuse bone pain, aggravated for the last 3 months, with the onset of FI, evolving in a context of AEG.
– Phosphocalcic assessment revealed: hypercalcemia = 133 phosphoremia = 21, vit D = 24, PTH = 96, elevated PAL and correct renal function.
– The check-up after vit D supplementation: hypercalcemia at 130 and PTH = 71.
– Cervical ultrasound: no abnormalities. Parathyroid cesta-MIBI scan: no argument in favor of a pathological parathyroid gland.
– A whole body scan with technetium-99m methyldiphosphonate (Tc-99m MDP) was performed, showing heterogeneity of global fixation of the radiotracer on the whole axial and peripheral skeleton with an attenuation of the renal shadows evoking the "super bone scan".
– In the sense of bone metastases: RT: asymmetric prostate, firm, bulging on the left side, ultrasound: prostatic hypertrophy at 42 cc heterogeneous seat of calcifications, PSA elevated at 9.8 with a free PSA/total PSA ratio = 0.25 = a prostate biopsy is planned.

Discussion
– The "super bone scan" situations can be related to metabolic pathologies (especially hyperparathyroidism) or secondary: a bone diseases either metastatic (prostate/breast cancer), or myeloproliferative disorders.
– The PTH values in this patient are not comfortable for the diagnosis of hyperparathyroidism (primary/parathyroid carcinoma). And given the context (age, AEG, high PSA), we consider the diagnosis of paraneoplastic hypercalcemia. What about the image of parathyroid fixation on FDG PET? - Considering the high number of false positives on FDG-PET and the low risk of false negatives on cesta-MIBI scintigraphy.
– The most probable diagnosis is considered to be: malignant hypercalcemia in the context of a paraneoplastic syndrome on bone metastases of a prostatic ADK. And that the parathyroid fixation on PET scan is a false positive.
Conclusion
– The "super bone scan" is a peculiar condition characterized by extremely high bone uptake compared to soft tissue, with no visualization of renal radioactivity.
– May be of metabolic or secondary origin.
– The etiological diagnosis must take into account the clinical context and discuss on a case-by-case basis.

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EP220

A rare cause of hypocalcaemia: The clues were in the biochemistry

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Introduction
Pseudohypoparathyroidism (PHP) is a rare cause of hypocalcaemia due to parathyroid hormone (PTH) resistance in the proximal renal tubules. In contrast to PHP type 1A, PHP type 1B is characterised by the absence of the characteristic skeletal abnormalities and is transmitted in an autosomal dominant manner, but in the maternal line. Patients may have resistance to the action of other G-protein signaling hormones, like thyroid stimulating hormone (TSH).
Case Presentation
A 28-year-old male was admitted with intermittent bilateral arm pains, tingling and carpopedal spasms, ongoing for a few years. His calcium was 1.4 mmol/l (2.20-2.60); phosphate, 1.56 mmol/l (0.8-1.5); PTH, 26.3 pmol/l (1.6-6.9) and 25-hydroxy-vitamin D, 24 nmol/l (25-125). Alkaline phosphatase, magnesium, TSH and renal function were normal. There were no phenotypic features of Albright's Hereditary Osteodystrophy (notably normal 4th/5th metacarpals and height). There was no family history of calcium disorders. He reported being treated previously with Alfacalcidol, but had not taken this for years and remained asymptomatic. The hyperphosphataemia in the presence of elevated PTH with normal renal function suggested PTH resistance. His symptoms resolved with Alfacalcidol and calcium supplements. Genetic testing revealed he had pseudohypoparathyroidism type 1B: heterozygous deletion of exons 5-7 of the STX16 gene and complete loss of maternal methylation pattern at the GNAS A/B: TSS-differentiated-methylated region, the latter meaning this was maternally inherited. He had low 24-hour urinary calcium and phosphate: 0.3 mmol/24 hr (2.5-7.5) and 3.4 mmol/24 hr (15-50), respectively. The renal PTH resistance is confined to the proximal tubules with lack of PTH resistance in distal renal tubules or skeleton. This causes reduced urinary calcium and phosphate excretion with preserved skeletal calcium and phosphate mobilisation. This results in partial protection from symptomatic hypocalcaemia and an absence of skeletal abnormality.
Conclusion
PTH resistance should be suspected in patients with chronic hypocalcaemia, hyperphosphataemia, elevated PTH levels and normal renal function, prompting genetic confirmation.
Reference
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EP221

Our experience with the treatment of pseudohypoparathyroidism

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Pseudohypoparathyroidism (PHP) is a group of rare hereditary diseases caused by tissue resistance to parathyroid hormone (PTH), there are two main types I and II. Type I is divided into subtypes. The authors present a case of PHP Ib, with hypocalcemia (level of total calcium 1.41 mmol/l), accidentally detected at childbirth. After the unsuccessful treatment of hypocalcemia, the etiology was considered, but the confirmation of the diagnosis were not adequately tightened. Due to the subjective feeling of palpitations and tremors, she was also examined by a psychiatrist and antipsychotic treatment was started. The level of ionized calcium at the time of treatment initiation was 0.98 (1.03-1.30 mmol/l), total calcium 1.95 (2.18-2.60 mmol/l), parathyroid hormone level was 52.343 (10.5-7.632 pmol/l), the level of phosphorus was 1.360 (0.65-1.61 mmol/l) and the level of vitamin D3 (25-OH) was 33.460 (75-250 nmol/l). Years later, PHP Ib has been genetically proved. By adjusting the proper treatment, including the administration of calcitriol 0.25 ug twice a day, calcium carbonate 1500 mg once a day and chronic treatment, the difficulties subsided. Control level of ionized calcium was 1.16 mmol/l, total calcium was 2.34 mmol/l, and the parathormone level was adjusted to normal 15.762 pmol/l. The effect of PTH on bone was reduced, which is expected to improve the prognosis to the level of the population.
Keywords: hyperphosphatemia, hypocalcemia, parathyroid hormone, pseudohypoparathyroidism.

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EP222

Femoral fracture revealing primary hyperparathyroidism in a very young patient and multiple lytic bone lesions: A case report

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Introduction
Primary hyperparathyroidism is the most common endocrinopathy after diabetes and thyroid diseases. Most often, the diagnosis is made at the asymptomatic stage due to the frequent phosphocalcic assessment objectifying hypercalcemia. Much more rarely, primary hyperparathyroidism is diagnosed at the stage of digestive, renal or bone complications. We report the case of a young patient with a femoral fracture that revealed primary hyperparathyroidism.
Observation
A 31-year-old male patient with a history of a left leg fracture at the age of 23 years, admitted to the endocrinology department for the management of acute hypercalcemia at 145 mg/l discovered during a workup for a femoral fracture following a simple fall at home. A CT scan of the pelvis revealed a displaced complex fracture of the left femoral neck, with multiple lytic bone lesions, involving the pelvic girdle and the left femur with cystic density. A complementary thoracic-abdominal-pelvic CT scan showed multiple thoracic-abdominal-pelvic lytic bone lesions. The etiological workup revealed a profile of primary hyperparathyroidism, with a left inferior parathyroid adenoma on topography. The patient underwent stabilization of the fracture site by nailing, followed by adenomectomy with bone biopsy, which revealed lesions consistent with hyperparathyroidism.
Discussion and Conclusion
Primary hyperparathyroidism is the consequence of excessive and inappropriate production of parathyroid hormone. It is often caused by a single or multiple parathyroid adenoma. Its revelation by fracture is very rare as it is the case in our patient. The associated bone lesions are often fibrocystic osteitis lesions due to the hyperactivity of osteoclasts, observed in hyperparathyroidism. Management is based on consolidation of the fracture and removal of the secretory adenoma. Every practitioner should consider the diagnosis of primary hyperparathyroidism at the stage of bone pain before complications development.

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EP223

Osteoporosis secondary to diabetes mellitus

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Introduction
Osteoporosis is a generalized skeletal disease that combines a decrease in bone density with changes in bone microarchitecture. The bone is abnormally fragile

and therefore the risk of fracture is high. We report the case of osteoporosis in a young woman secondary to type 1 diabetes mellitus (T1DM).
Case Report
Patient A.M, 26 years old, with a history of polyglandular autoimmune syndrome type 3 since the age of 12, associating T1DM and Hashimoto's thyroiditis, was admitted to hospital for investigation of a spontaneous fracture of the right carpal bone. Bone densitometry (BMD) showed a T score of -3.4 standard deviations (SD) in the spine and -2.6 SD in the femoral neck, confirming the diagnosis of osteoporosis. The etiological investigation was negative. Metabolic, pharmacological, endocrine (hyperthyroidism/hyperparathyroidism), hormonal, deficiency (osteomalacia) and nutritional causes were ruled out and the diagnosis of osteoporosis secondary to diabetes mellitus was retained.
Discussion/Conclusion
Chronic hyperglycaemia adversely affects bone by altering qualitative and quantitative bone formation due to the direct toxic effects of glucose on the osteoblast. In addition, diabetes leads to impaired microcirculation which may interfere with bone repair. Most studies have shown a decrease in BMD in patients with diabetes. Diabetes is therefore associated with an increased risk of fracture through osteoporosis. These findings should be kept in mind for optimal management of our patients with diabetes.

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Diabetes, Obesity, Metabolism and Nutrition

EP224

The role and potential mechanism of long noncoding RNA ENST0000052114 in differentiation of human preadipocyte

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Obesity, as a chronic nutritional disorder, is a high-risk factor for type 2 diabetes, fatty liver and other metabolic diseases. Multiple lncRNAs have been confirmed concerning adipocyte differentiation and thus affect obesity, such as ADINR, Paral1, etc. Previously, we identified a lncRNA named ENST0000052114 (abbreviated to lncRNA52114), highly expressed in human mature adipocytes by differential lncRNA expression profile. Here, we explored the role and mechanism of lncRNA52114 in the differentiation of human preadipocytes from visceral adipose (HPA-vis). Over-expressed or silencing lentiviral vector of lncRNA52114 was constructed. After transfection of precursor cells, the infection efficiency of lentivirus was observed by fluorescence microscope and was verified by qPCR. The classical induction protocol (1-methyl-3-isobutylxanthine, dexamethasone, insulin, and rosiglitazone) was used to induce HPA-vis to mature adipocytes. The morphology and lipid droplet size of adipocytes were detected by oil red O staining, and the content of triglyceride was detected by chemiluminescence method. qPCR and Western Blot were used to detect the mRNA and protein expression levels of adipocyte differentiation (PPARγ, C/EBPα, C/EBPβ, FABP4, etc.). Compared with the control groups, there was no significant change in oil red O staining, triglyceride content, differentiation marker genes expression levels in the lncRNA52114 overexpression groups. On the contrary, the silence of lncRNA52114 expression can significantly inhibit the differentiation rate of HPA-vis compared with the control groups, which is manifested by the decrease of the lipid droplets number and triglyceride content in mature adipocytes. The mRNA and protein expression levels of C/EBPα, C/EBPβ and FABP4 were significantly downregulated in silence group. Fluorescence in situ hybridization (FISH) showed that lncRNA52114 was highly expressed in nucleus and also in cytoplasm. RNA transcriptome sequencing found that the differentially expressed genes were mainly concentrated in the thyroid hormone synthesis pathway (TSHR, GPX3, etc.). Among those genes, TSHR was significantly reduced after lncRNA52114 silencing and closely related to adipocyte differentiation. Overexpression of TSHR on the basis of lncRNA52114 silencing can reverse the effect of its silencing on adipocytes differentiation. CUT&TAG and CUT&RUN showed that lncRNA52114 can decrease the enrichment level of H3K4me3 in TSHR promoter region. LncRNA52114 may influence the differentiation of adipocytes by downregulating the TSHR histone modification in the thyroid hormone synthesis signaling pathway. This study will provide a new theoretical basis and experimental evidence for the study of adipocyte differentiation and a potential target for the prevention and treatment of obesity.

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EP225

The closest results of the autologous mesenchymal stem cell transplantation in patient with type 1 diabetes mellitus in the honeymoon phase

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Background and Aims
The type 1 diabetes mellitus (T1DM) remains one of the main public healthcare problems worldwide. Recent clinical studies have shown a promising stem cell role in the treatment of T1DM. We evaluated the closest therapeutic effect of autologous mesenchymal stem cell transplantation (AMSCT) on carbohydrate metabolism markers in type 1 diabetes mellitus (T1DM) patient in the honeymoon phase.
Materials and Methods
C-peptide (ng/ml), glycated hemoglobin (HbA1C,%), fructosamine (μmol/l), daily insulin dosage (Units/day) were analyzed in the 19-year- old woman (BMI 20.8 kg/m^2) with 7 month history of T1DM with positive islet-cell antibodies (ICA-8.74) before and 6 weeks after AMSCT (cells were obtained from the patients iliac crest and were cultivated for 3 weeks) by intravenous infusion. The quantity of autologous mesenchymal stem cells infused was from $95\text{-}97\times10^6$.
Results
AMSCT 6 weeks after led to increase C-peptide from 0.58 ng/ml to 1.72 ng/ml (normal range: 1.1-4.4 ng/ml), decrease in daily insulin dosage levels from 18 Units/day (0.38 Unit/kg) to 7 Units/day (0.15 Unit/kg) with trend to decrease HbA1c and fructosamine levels, from 8.07% to 7.26% and 320.6 μmol/l to 266.59 μmol/l (normal range: 205.0-285.0 μmol/l), respectively.
Conclusion
The AMSCT in patient with type 1 diabetes mellitus in the honeymoon phase results in an increase in the C-peptide level as well as a decrease of the daily insulin dose, with trends towards a decrease in glycated hemoglobin and fructosamine 6 weeks after transplantation.

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EP226

Impact of Hybrid Closed-Loop Systems on Diabetes Management Compared to Sensor-Assisted Pump Systems

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Background and Aim
Over the past years, hybrid closed-loop (HCL) systems have emerged as the state-of-the art treatment of type 1 diabetes (T1D), and there is sufficient evidence to support their safety and value. The aim of this review was to evaluate all the available literature regarding the impact of HCL systems on diabetes management compared to sensor augmented pump (SAP) systems.
Methods
An extensive literature search was conducted through electronic databases (PubMed, Scopus and CINAHL) with the terms 'hybrid closed-loop systems, 'automated insulin dosing systems, 'sensor augmented pump systems' and 'time in range'. Articles published in English, until September 2022, were included; no other criteria on publication dates were set.
Results
A total of 29 studies were included. Eleven studies investigated the effect of the HCL system in adult patients, 7 studies in adult, adolescent, and pediatric patients and 11 studies in pediatric and adolescent patients. The HCL systems used were the Minimed 640G, Minimed 670G, Minimed 780G, Bionic pancreas, Diabeloop, Dana-i and Tandem t: slim. Twenty-seven studies showed statistically significant reduction in mean glucose and a significant increase in the percentage of time within target range in HCL group compared to SAP. In addition, a significant reduction in average HbA1c levels was reported by 14 studies in HCL group compared to the SAP group. Time spent in hyperglycemia and hypoglycemia were significantly reduced in HCL group in 15 studies.
Conclusions
Hybrid closed-loop insulin delivery systems provide better glycemic control and more time in range compared to SAP systems. Therefore, the HCL system represents an important treatment option for patients with T1D.

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EP227

Disorders of microcirculatory haemostasis in adolescents with tipe 1 diabetes mellitus

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Microcirculatory disorders play important role in pathogenesis of diabetic vascular complications.
Aim
to study peculiarities of microcirculatory haemostasis (tromboresistance of vessel wall and functional activity of thrombocytes) in adolescents with type 1 diabetes mellitus (T1DM).
Patients and methods
120 adolescents (55 boys, 65 girls) 12–17 y.o. with T1DM were examined. The duration of the disease was: less than 1 year - in 42 patients (HbAc1 7.4 ± 0.5%) – group 1, from 1 to 5 years - in 46 patients (HbAc1 8.3 ± 1.2%) – group 2, more then 5 years - in 32 patients (HbAc1 10.2 ± 1.1%) – group 3. Control group: 110 healthy adolescents 12-17 y.o. The indexes of tromboresistance of vessel wall (antiaggregating, anticoagulating, antifibrinolytic activity) measured by manjetic method. The indexes of trombocyte aggregation (degree, speed and time of aggregation) measured by laser method with different inductors (ADP, adrenalin, kollagen) and intravascular aggregation were evaluated.
Results
tromboresistance of vessel wall was normal in group 1 in comparance of control group ($P < 0.05$). Levels of ADP- and adrenalin-stimulating aggregation, intravascular aggregation of thrombocytes were increased in this group ($P < 0.05$). Tromboresistance of vessel wall was decreased in group 2 ($P < 0.05$). Levels of ADP- and kollagen-stimulating aggregation ($P < 0.05$) and intravascular aggregation ($P < 0.05$) were also increased in group 2. Decrease of aggregation time was revealed in this group ($P < 0.05$). Decrease of tromboresistance of vessel wall ($P < 0.001$), increase of all indexes of functional activity of thrombocytes ($P < 0.05$) and intravascular aggregation ($P < 0.001$) were found in patients of group 3 in comparance of control group.
Conclusions
Microcirculatory disorders in adolescents with T1DM correlated with duration of the disease and may demand treatment.

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EP228

Importance of MMP-2 and MMP-9 gene polymorphism in the delopment of microvascular complications in type 2 diabetes patients

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Background
Vascular complications are leading cause of increased morbidity and mortality of diabetic patients. Pathophysiological mechanisms included in the development and progression of diabetic complications are various and lately it has been postulated that matrix metalloproteinases MMP-2 and MMP-9, zinc-dependent endopeptidases through remodeling of extracellular matrix can contribute to the onset and progression of diabetic vascular complications. The aim of our study was to assess whether there is a major difference in single nucleotide polymorphisms in the MMP-2 (at position -1306C > T) and MMP-9 (at position -1562C > T) gene in type 2 diabetic patients and healthy controls and to determine whether there is association of these gene variants with the presence of microvascular complications in diabetic patients.
Methods
Our study included 102 type 2 diabetes patients and control group which comprised 56 healthy controls. All diabetic patients were screened for microvascular diabetes complications. Genotypes were detected by polymerase chain reactions followed by restriction analyses with specific endonucleases (PCR-RFLP) and their frequencies determined.
Results
MMP-2 gene variant -1306C > T showed negative correlation with the presence of T2DM ($P = 0.042$). It was shown that presence of allele -1306C increases the probability of developing type 2 diabetes 2.1 times and that allele -1306 T has protective role regarding type 2 diabetes. MMP-2 variant -1306T showed negative correlation with diabetic polyneuropathy ($P = 0.017$) which means that allele-1306T has protective role regarding diabetic polyneuropathy while presence of allele -1306C increases the probability of developing diabetic polyneuropathy 3.2 fold.
Conclusion
To our knowledge, this is the first study investigating MMP2 and MMP9 genetic variants and all three microvascular complications. Our study showed that MMP-2 gene variant (-1306C) doubles the risk of developing type 2 diabetes and for the first time showed association of this gene variant and presence of diabetic polyneuropathy.

Keywords: diabetes mellitus, matrix metalloproteinase-2 and -9, SNP (single nucleotide polymorphism), microvascular complications, diabetic polyneuropathy.
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EP229

The role of vitamin D in reducing colorectal cancer risk and progression

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Introduction
In addition to its role in phosphocalcic metabolism, the vitamin D (vitD) seems to have anti-tumor effects, particularly in colorectal cancer (CRC). The active metabolite of vitD [1,25$(OH)_2D_3$], converted by the enzyme CYP27B1, inhibits proliferation and promotes differentiation of CRC cells which express vitamin D receptor (VDR) via the regulation of a high number of genes. The vitD metabolism seems also to regulate inflammatory processes involved in CRC development and progression, including the $CD4^+$ T cells differentiation and the cytokines production. This study aimed to investigate VitD related parameters and Th17-related parameters in CRC patients in comparison with controls.
Patients and Methods
This is a case-control study including 43 untreated CRC patients and 86 healthy controls. The expression levels of *VDR, CYP27B1* and interleukin 23 receptor (*IL-23R*) genes in peripheral blood mononuclear cells (PBMC) were studied using a quantitative PCR (qPCR). The measurement of circulating levels of VitD (25(OH)D) and IL-17A was performed using ELISA kits.
Results
The mean level of circulating 25(OH)D was significantly lower in CRC patients in comparison with controls (13.77 ± 7.93 vs 21.07 ± 8.79; $P = 0.002$, respectively). A statistically significant association was observed between VitD deficiency (25(OH)D < 20 ng/ml) and risk of CRC (OR = 6.42; IC 95% = 2.64 et 15.61; $P < 0.001$). In contrary, the mean levels of *VDR* and *CYP27B1* gene expression were significantly higher in patients than in controls ($P = 0.002$; $P = 0.047$, respectively). Regarding Th17 axis, the mean level of circulating IL-17A was significantly higher in patients than in controls ($P = 0.009$). The mean level of *IL-23R* gene expression was higher in patients than in controls ($P = 0.1$). The levels of 25(OH)D were inversely correlated with the circulating levels of IL-17A ($r = -0.33$; $P = 0.03$). Furthermore, the circulating levels of IL17A were positively correlated with the gene expression levels of *VDR* and *CYP27B1* ($r = 0.33$; $P = 0.035$ and $r = 0.39$; $P = 0.012$, respectively).
Conclusion
The vitD, by binding to its receptor (VDR), seems to regulate the expression of a high number of genes involved in CRC cell proliferation as well as T helper cell differentiation. Further clinical studies are required to confirm the close interplay between vitD, anti-tumor immunity, and CRC, suggesting a possible role of vitD as a potential agent in CRC prevention and therapy.

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EP230

The impact of type 2 diabetes on the post-COVID period according to the ACTIV SARS-CoV-2 registry

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Background
SARS-CoV-2 profoundly impacts population health through both acute infection and post-COVID period. Multiple studies make it clear that metabolic diseases can significantly affect the course of COVID-19.
Aim
To study the course of post-COVID period in patients with type 2 diabetes mellitus (DM2).
Methods
The international registry ACTIV SARS-CoV-2 (NCT04492384) was established to study COVID-19 in the Eurasian region. The post-COVID period was assessed based on telephone surveys of the patients 3 months ($n=3083$), 6 months ($n=2485$) and 12 months ($n=1774$) after recovery. DM2 was reported in 14.3% ($n=441$), 15% ($n=373$) and 14.2% ($n=252$) of all respondents, respectively.
Results
One or more complaints/symptoms (general weakness, dyspnea, unstable blood pressure, arrythmia, cough, thoracalgia, arthralgia, olfaction disorders, myalgia, lower limb edema) persisted more often in patients with DM2 compared to patients without DM2 within 12 months after recovery. At the same time, the proportion of patients with complaints/symptoms gradually increased over time (Table 1). Sub-analysis of 1416 patients at 3 months, 1110 patients at 6 months, and 702 patients at 12 months after recovery demonstrated that DM2 was associated with more unscheduled care visits after recovery (Table 2). Finally, mortality was elevated, and the adverse outcome rate was the highest in patients with type 2 diabetes at 12 months after recovery (Table 3).
Conclusion
DM2 in COVID-19 patients contributes to longer persistence of complaints/-symptoms, need for unscheduled medical care, and mortality within 12 months after recovery. These findings call for active monitoring, a more detailed examination, and rehabilitation of patients with DM2 in the post-COVID period.

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EP231

Neurotropic properties of high- and low-selective sodium-glucose cotransporter type 2 inhibitors in type 2 diabetic patients

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Background and Aim
Type 2 diabetes mellitus (DM) treatment guidelines give preference to drugs with proven cardioprotective effect, which include sodium-glucose cotransporter type 2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA). GLP-1RA are known to reduce the stroke risk. Data on SGLT-2i effect on the brain, in conditions of both acute and chronic cerebrovascular disorders, are less complete. The aim of our study was to evaluate the effect of high-selective SGLT-2i empagliflozin (EMPA) and low-selective SGLT-2i canagliflozin (CANA) on the central nervous system biochemical and functional parameters in type 2 diabetic patients.
Materials and Methods
The study included type 2 DM patients aged 45-75 on metformin monotherapy. The following groups were formed: group 1 ($n=12$) - patients with target glycated hemoglobin (HbA1c) level who did not undergo therapy correction, groups 2 and 3 ($n=14$ and $n=12$, respectively) - patients with HbA1c exceeding target no more than 2.5%. In group 2 EMPA therapy was initiated, in group 3 CANA therapy. Control group ($n=18$) of healthy volunteers was also created. In all groups, the levels of HbA1c, neuron-specific enolase (NSE), neurofilament light chains (NLC) were determined initially, cognitive assessment scales (MOCA, MMSE) were used. In groups 2 and 3 these parameters were also evaluated after 3 and 6 months.
Results
Baseline NSE level in DM patients was higher than in healthy volunteers, regardless of glycemic control (2.76 (2.47; 3.92) ng/ml in the control group, 3.22 (2.61; 4.16) ng/ml in DM with target HbA1c, 3.58 (3.11; 3.73) ng/ml in DM with non-target HbA1c). EMPA addition did not cause changes in NSE, while CANA administration significantly reduced NSE (after 6 months it was 2.73 (2.00; 2.92) ng/ml). The NLC in DM patients with target HbA1c initially did not differ from that in control group (4.5 (3.31; 5.56) and 4.13 (3.31; 5.31) ng/ml, respectively), but was elevated in patients with non-targeted HbA1c (5.25 (3.75; 6.25) ng/ml). Both EMPA and CANA caused this parameter decrease, while CANA effect was more pronounced - NLC after 6 months of EMPA therapy was 4.50 (3.45; 4.50) ng/ml, CANA - 2.00 (1.95; 2.20) ng/ml. DM, even with target HbA1c, led to cognitive deficits when assessed by MOCA and MMSE. EMPA and CANA significantly improved these parameters over time. Negative correlation was found between NLC level and the points in MOCA and MMSE.
Conclusions
DM, even with satisfactory glycemic control, has a negative impact on the brain, which is manifested by neuronal damage markers increase and cognitive dysfunction. High- and low-selective SGLT-2i have a neuroprotective effect, which is probably more pronounced in low-selective CANA.

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The effect of glycemic environment on bone mineral density in patients with type 1 diabetes mellitus

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Introduction
Hyperglycemia in type 1 diabetes mellitus (T1DM) is an important determinant of bone health. However, data on the effect of glycemic changes on bone metabolism

Table 1 (Abstract EP230). Persisting complaints/symptoms rate in the post-COVID period

	3 months		6 months		12 months	
	No complaints/ symptoms	Persisting complaints/ symptoms	No complaints/ symptoms	Persisting complaints/ symptoms	No complaints/ symptoms	Persisting complaints/ symptoms
Without DM2, *n*	1201 (89.8%)	1441 (82.5%)	1088 (88.5%)	1024 (81.6%)	965 (88.7%)	557 (81.2%)
With DM2, *n*	136 (10.2%)	305 (17.5%)*	142 (11.5%)	231 (18.4%)*	123 (11.3%)	129 (18.8%)*

Note: *$P<0.001$.

Table 2 (Abstract EP230). Unscheduled healthcare visits in the post-COVID period

	3 months		6 months		12 months	
	No visits	At least 1 visit	No visits	At least 1 visit	No visits	At least 1 visit
Without DM2, *n*	255 (89.2%)	911 (80.6%)	209 (90.1%)	681 (77.6%)	217 (87.9%)	366 (80.4%)
With DM2, *n*	31 (10.8%)	219 (19.4%)*	23 (9.9%)	197 (22.4%)*	30 (12.1%)	89 (19.6%)**

Note: *$P<0.001$, **$P=0.011$.

Table 3 (Abstract EP230). Mortality in the post-COVID period

	3 months		6 months		12 months	
	Survived	Died	Survived	Died	Survived	Died
Without DM2, *n*	2642 (85.7%)	43 (74.1%)	2112 (85.0%)	12 (92.3%)	1522 (85.8%)	5 (41.7%)
With DM2, *n*	441 (14.3%)	15 (25.9%)*	373 (15.0%)	1 (7.7%)**	252 (14.2%)	7 (58.3%)***

Note: *$P=0.022$, **$P=0.520$, ***$P=0.001$.

are limited. The aim of this study was to evaluate BMD in patients with T1DM in relation to changes of glycemic control.
Methods/Design
We studied 118 uncomplicated patients with T1DM (GroupD) (mean age: 30.12 + 8.78years, F/M: 65/53) and 94 healthy controls (GroupC) matched for age, sex and body mass index (BMI). All patients in GroupD were re-examined after 18 months (FU). In both groups, we measured HbA1c and BMD at lumbar spine (LS), total hip (TH) and femoral neck (FN) by dual energy X-ray absorptiometry (DXA). HbA1c changes of $\geq$ 0.5% were considered significant. For BMD changes to be considered significant a minimum change of 3% at LS, 3.3% at TH and 4.7% at FN is needed.
Results
At baseline, in GroupD mean duration of diabetes was 16.16 + 9.56 years, mean HbA1c was 7.94 + 1.37% and absolute values of BMD (g/m^2) were significantly lower at LS, TH and FN compared to GroupC ($P = 0.018$, $P < 0.001$ and $P = 0.007$, respectively). At FU, in GroupD mean HbA1c was 7.93 + 1.59% and BMD changes from the baseline were: at LS: -1.4%, TH: -1% and FN: -2.0%. In FU, males in GroupD appeared to have greater decreases in BMD than females (M: LS: -2.2%, TH: -3.3% and FN: -4.1%. vs F: LS: -0.8%, TH: -0.9% and FN: -0.8%) . There was a significant negative correlation between HbA1c changes and TH BMD changes ($r = -0.233$, $P = 0.02$).
Conclusion
Worsening glycemic control is associated with reduction in BMD in patients T1DM, and it seems that males are more affected than females.

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EP233

Metabolically healthy non-alcoholic fatty liver disease and progression of coronary artery calcification: A 15 year longitudinal study

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Objective
Non-alcoholic fatty liver disease (NAFLD) is considered as a continuum from obesity and metabolic syndrome (MetS). To investigate the cardiovascular prognosis of metabolically healthy NAFLD, this study aimed to evaluate the association between NAFLD with and without MetS and change in coronary artery calcification (CAC).
Methods
This is a retrospective longitudinal study of 5,117 subjects without cardiovascular disease who participated in a health screening program. Ultrasonographic measurements of fatty liver and multi-detector computed tomography were concurrently performed to determine the CAC score. We classified the subjects into four groups according to NAFLD status and MetS presence: controls neither NAFLD nor MetS, NAFLD without MetS, MetS without NAFLD, and NAFLD with MetS. CAC progression was defined as [$\sqrt{}$CAC score (follow-up) $-$ $\sqrt{}$CAC score (baseline)] $\geq$2.5.
Results
During median follow-up of 5.0 years, CAC progression was detected in 2,125 subjects (41.1%). After adjustment for age, diabetes, hypertension, triglycerides, HDL-cholesterol, use of lipid-lowering drugs, smoking status, and baseline CAC score, the hazard ratios (HRs) for CAC progression comparing controls, those of NAFLD without MetS, MetS without NAFLD, and NAFLD with MetS were 1.21 (95% CI: 1.08–1.35), 1.04 (0.85–1.27) and 1.36 (1.15–1.56), respectively. When NAFLD without MetS were stratified by the severity of ultrasonographic findings, subjects with moderate to severe NAFLD had a higher risk of CAC progression, compared to those without NAFLD or mild NAFLD. The prognostic factors for CAC progression were higher HbA1c, fasting plasma glucose, aspartate transaminase, γ-glutamyltransferase, and baseline CAC score in subjects with metabolically healthy NAFLD.
Conclusions
NAFLD without MetS was significantly associated with an increased risk of CAC progression regardless of other cardiometabolic risk factors. NAFLD without MetS might be considered to have an intermediate metabolic phenotype between healthy individuals and NAFLD patients with MetS.

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Influence of metabolic factors on the course of the acute period of COVID-19 in hospitalized patients according to the international registry ACTIV SARS-CoV-2

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Background
The literature shows that body mass index (BMI) and blood glucose levels can significantly influence the course of infectious diseases. In the light of ongoing SARS-CoV-2 pandemic, its rational treatment and prevention are strategic public health goals.
Aim
To study the relationship between BMI and serum glucose levels during the acute period of COVID-19 in hospitalized patients.
«ACTIV SARS-CoV-2» registry was established to evaluate the course of COVID-19 in the Eurasian region and covered 7 countries. ACTIV (NCT04492384) and ACTIV 2 (NCT04709120) are multicenter non-interventional real-world registries. 6396 subjects from ACTIV and 2968 subjects from ACTIV 2 were included in this study.
Results
Patients with higher serum glucose levels and BMI had significantly more severe acute period of COVID-19, characterized by acute kidney injury (AKI), hyperinflammatory syndrome, increase in C-reactive protein (CRP) above 100 mg/l, or need for targeted therapy (Table 1).Moreover, hyperglycemia at 6.9 (5.6–9.18) mmol/l was significantly ($P < 0.001$) associated with death in the acute period (versus 5.7 (5.0–7.0) mmol/l in the survivors).
Conclusions
Analysis of the ACTIV SARS-CoV-2 registry showed that patients with a more severe course of the acute period of COVID-19 in the form of AKI, "cytokine storm", increase in CRP above 100 mg/l, or need for targeted therapy had higher serum glucose levels and BMI. In addition, hyperglycemia was associated with death during hospitalization for SARS-CoV-2. These findings allow the studied clinical parameters to be used as characteristics of the severe course of the disease.

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EP235

The role of microbiome features in postprandial blood glucose response in patients with gestational diabetes

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Table 1 (Abstract EP234). Severity of Acute COVID-19 by Serum Glucose Levels and BMI

Characteristics of acute COVID-19	Metabolic factor	Absent Me (Q1 – Q3)	Present Me (Q1 – Q3)	*P*
AKI	Glycemia, mmol/l	5.8 (5.0–7.0)	6.0 (5.2–8.55)	0.011
	BMI, kg/m^2	27.8 (24.8–31.6)	29.6 (25.1–33.5)	0.018
"Cytokine storm"	Glycemia, mmol/l	5.7 (5.0–6.6)	6.1 (5.2–8.0)	<0.001
	BMI, kg/m^2	27.5 (24.4–31.2)	28.7 (25.6–32.8)	<0.001
CRP above 100 mg/dl	Glycemia, mmol/l	5.4 (4.8–6.7)	6.1 (5.0–8.1)	<0.001
	BMI, kg/m^2	27.7 (24.7–31.7)	28.7 (25.5–32.7)	<0.001
Need for targeted therapy	Glycemia, mmol/l	5.8 (5.0–7.1)	6.3 (5.4–8.0)	<0.001
	BMI, kg/m^2	27.7 (24.7–31.3)	29.7 (26.3–34.2)	<0.001

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Background and Aims
The gut microbiome has been shown to differ between healthy individuals and those with diabetes and even in women with gestational diabetes mellitus (GDM). This raises the question of its role in postprandial glycemic response (PPGR). We aimed to evaluate the impact of microbiome features in PPGR in women with GDM and healthy pregnant women.
Methods
We obtained stool samples for 96 pregnant women (65 GDM, 31 control), previously recruited for GEM-GDM study (NCT03610178), who consented to continuous glucose monitoring (CGM) for 7 days (31.5±3.1 weeks) and provided relevant food diaries. After additional filtering for quality diaries and number of food intake records per person, 45 women were selected for the statistical analysis. CGM data were analyzed with records of 720 meals. Stool samples were collected within 1-2 weeks after recruitment (28.8±3.6 weeks).16S rRNA gene sequence analysis was carried out after sequencing on a MiSeq platform. 780 bacterial features were selected after the following filters were applied: by the frequency of occurrence of the feature in the samples (at least three) and by the number of copies of the bacterial feature (at least 20). The Shapley additive explanations method was implemented to evaluate feature importance.
Results
When microbiome data were added to the input parameters of the model, the greatest contribution to PPGR was made by the abundance of bacteria of the genera *Ruminococcus* and *Bacteroides*. Their greater relative abundance was associated with an increase in the peak glycemic level after a meal. The contribution of bacterial traits to the accuracy of PPGR prediction depended on the choice of prediction algorithm and method of diary filtering. Models built with the addition of microbiome data showed better prediction accuracy in cross-validation datasets and on new patient data in predicting peak glycemic levels and 1-hour postprandial glucose levels. Inclusion of the microbiome data slightly increased the accuracy for predicting peak glycemic levels (mean absolute error 0.484 mmol/l vs 0.497 mmol/l for the models with and without microbiome data) and correlation between actual and predicted values ($R=0.718$ vs $R=0.704$) based on the full dataset ($n=96$), but did not change the accuracy in the more strictly filtered dataset ($n=45$).
Conclusions
Bacteria of the genera *Ruminococcus* and *Bacteroides* made the greatest contribution to peak postprandial glycemic level in pregnant women with GDM.

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Identification of predictors of severe hypoglycemia in adults with type 1 diabetes in andalusia (Spain): results of the multicenter study "Sehypan"

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Objectives
To describe modifiable sociodemographic and clinical risk factors predictive of severe hypoglycemia with need for urgent health care in adults with type 1 diabetes (T1DM).
Methods
Multicenter, observational and retrospective study with case-control design.
Cases
T1DM adults with severe hypoglycemia, defined as glycemia <70 mg/dl requiring urgent out-of-hospital health care for its resolution. Data source, geographical and temporal framework: cases selected from the register of care contacts of the Public Emergency Company of Andalusia (PECA) throughout the territorial scope of the Andalusian Public Health System (APHS), during the period 2018-2020.
Controls
Adults with T1DM without a history of severe hypoglycemia. Selected with 1:1 ratio, matched by basic variables: sex, age, reference health area, glycemic monitoring method and insulin administration system (multiple doses/insulin pumps).
Results
A total of 389 participants were included (219 cases and 170 controls) from a total of 16 reference hospitals in Andalusia (Spain). The mean age of the cases was 46.4 years (SD 14.2), with 57.5% male. The most frequent cause of severe hypoglycemia was an error in rapid insulin dosing (33.8%). In 15.6% of the cases, evacuation to a health center was required for resolution. More than one severe hypoglycemia event was recorded during the study period (2018-20) in 35.5%. In 18.9% of cases used interstitial flash glucose monitoring systems at the time of severe hypoglycemia, and 3.8% were users of insulin pumps. Among the psychosocial variables, a higher prevalence of depression (17.7% vs 7.1%, $P=0.007$), physical and/or intellectual disability (9% vs 3%, $P=0.04$) and lack of university or technical education (59.7% vs 36.8%, $P=0.002$) was observed in the group of cases. In relation to the natural history of T1DM, the time of evolution was longer in cases compared to controls (27.9 vs 23 years, $P=0.008$), as well as the prevalence of chronic complications (proliferative retinopathy 16.8% vs 6.3%, $P=0.007$; vascular-cerebral accident 6.2% vs 0.8%, $P=0.01$) and of NO follow-up in endocrinology units (14.2% vs 7%, $P=0.04$). The previous history of severe hypoglycemia was significantly higher in the case group, both in the overall follow-up history and in the last year (respectively: 56.4% vs 16.5%, $P<0.001$; 34.5% vs 1.6%, $P<0.001$). Also higher in cases was the prevalence of nocturnal hypoglycemia (56% vs 26.9%, $P<0.001$) and of inadvertent hypoglycemia (61.6% vs 21.2%, $P<0.001$).
Conclusions
Chronic diabetes-related complications, history of severe hypoglycemia, nocturnal hypoglycemia and inadvertent hypoglycemia, as well as depression, dependency status and low academic education level are risk factors for severe hypoglycemia in T1DM. These variables could be incorporated into strategies for identifying patients at risk and designing specific preventive interventions based on diabetes education.

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The influence of advanced glycation end-products (AGEs) on diabetic retinopathy progression

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Background
Diabetes-induced prolonged elevated plasma glucose levels result in the formation and accumulation of complex and heterogeneous groups of compounds - advanced glycation end-products (AGEs). AGEs normally accumulate slowly, but this process occurs at a faster rate in patients with conditions such as diabetes or cardiovascular disease. Accumulation of AGEs increases oxidative stress and induces an inflammatory reaction, which has a significant influence on the exacerbation of diabetic vascular complications. One of the most common complications resulting from uncontrolled diabetes is diabetic retinopathy

(DR). However, it is necessary to clarify the role of AGEs in the pathology of DR to improve the quality of life for diabetic patients.
Aim
The aim of this study was to investigate the relationship between AGEs levels and DR progression.
Materials and Methods
120 patients (age $\geq$18) with type 1 (T1D) and type 2 diabetes (T2D), were enrolled. Patients were divided into 3 groups: no diabetic retinopathy (n=50), non-proliferative diabetic retinopathy (n=49), and proliferative diabetic retinopathy (n=11). AGEs levels in the skin were non-invasively measured with AGE Reader (Diagnoptics B.V., The Netherlands). Data on patients' clinical characteristics were collected from medical records.
Results
The median diabetes duration of the patients was 14.5 years, age – 55 years. The study cohort consisted of 64 (58.2%) women and 46 (41.8%) men. Patients with a longer duration of diabetes had more severe form of diabetic retinopathy ($P<$ 0.001). Age and HbA1c were comparable in groups with different severity of diabetic retinopathy (P=0.320 and P=0.094, respectively). However, the concentration of AGEs was higher in the group of patients with proliferative DR than in patients with non-proliferative DR and patients without DR ($P<$0.05). HbA1c levels were not related to AGEs concentration (P=0.354). AGEs levels increased with age (r=0.420, $P<$0.001) and duration of diabetes (r=0.331, $P<$ 0.001).
Conclusions
AGEs levels in the skin increase with progression of DR. These results support the evidence that AGEs have an important role as a prognostic biomarker for vascular risk assessment.
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A simultaneous pancreas-kidney transplantation for type 1 diabetes mellitus after a long-term period of hemodialysis (Clinical case)
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Introduction
Today simultaneous pancreas-kidney transplantation (SPKT) is an effective method of treatment for patients with type 1 diabetes mellitus (T1D) and terminal stage of diabetic nephropathy (DN) on renal replacement therapy by hemodialysis. It solves several problems: reduces the severity of intoxication syndrome, contributes to the achievement of euglycemia in most cases, that allows to delay progression of micro- and macrovascular diabetic complications.
Case Description
A 56-years-old Caucasian woman with T1D, end-stage renal disease (ESRD) underwent successful SPKT in October 2014 after 8 years haemodialysis therapy. T1D was diagnosed 34 years ago. Insulin therapy was initiated immediately, but glycemic compensation hadn't been achived after T1D onset due to lack of constant glycemic self-control (patient had 3 diabetic ketoacidosis, impaired awareness of hypoglycemia). Late diagnosis of DN (macroalbuminuria, uremia, blood pressure over 180/110 mm Hg since 2002) and late nephroprotective therapy prescription led to rapid progression of chronic kidney disease (CKD) to the terminal stage. Nonproliferative and proliferative diabetic retinopathy OS and OD respectively were diagnosed in 2011, neuropathic osteoarthropathy (DNOAP) of the right ankle joint - 2013. During 7 years after transplantation she is still euglycaemic without insulin therapy (glycated hemoglobin 5.7%, C-peptide 1.93 ng/ml) with creatinine of 70-90 µmol/l, estimated glomerular filtration rate 45.8 mL/min (stage 3a normoalbuminuric CKD), normal hemoglobin and blood pressure levels. Continuous glucose monitoring registrated hypoglycemic episodes (2.0 mmol/l). The tertiary hyperparathyroidism (HPT) treatment with cinacalcet stabilized calcium-phosphorus metabolism (corrected calcium for albumin 2.38 mmol/l, phosphate 1.03 mmol/l, parathyroid hormone 107.9 pg/ml, 25(OH)D 41.3 ng/ml), bone densitometry scores: T-score is $-$3.7 at the femoral neck, $-$2.0 L1-L4, -5.5 total radius. Surgical treatment of HPT was recommended. Patient received the standard triple immunosuppressive therapy, now receives double therapy. Despite euglycemia diabetes complications progressed to proliferative retinopathy OU, hemophthalmos OS, bilateral DNOAP in 2021. The patient has cardiovascular complications: cerebrovascular disease, atherosclerosis (stenosis of the right common carotid artery 35%, the right posterior tibial artery – 65%).
Conclusion
SPKT is the best treatment option for patients with T1D and ESRD. Unfortunately, even successful SPKT can't guarantee reverse development of diabetic complications, persisting at the moment of transplantation. The progression of complications may be associated with the continued influence of accumulated "metabolic memory" markers (advanced glycation end products (AGEs), receptor for AGEs, etc.). After transplantation such patients need strict control by nephrologist, endocrinologist, cardiologist, etc. to maintain positive results of euglycaemia and kidney function normalization.
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Neutrophil to lymphocyte ratio is associated with diabetic ketoacidosis in type 1 diabetes mellitus
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Introduction
Inflammation has been involved in the physiopathology of diabetic ketoacidosis (DKA). Hematological inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR) and white blood cell count (WBC) can serve as predictive markers for a systemic inflammatory response. This study aimed to evaluate hematological inflammatory markers in T1DM patients with DKA and without-DKA in an uninfected state and to determine their role in the prediction of DKA.
Patients and Methods
This is a retrospective preliminary study including a total of 30 T1DM uninfected patients. According to the onset characteristics, fasting blood glucose, ketone bodies, and blood gas analysis results, patients were divided into T1DM patients with DKA (n=7) and without-DKA (n=23) groups. Hematological inflammatory markers including WBC, NLR, PLR (platelet-to-lymphocyte ratio) and PNR (platelet-to-neutrophil ratio) were retrieved from complete blood counts.
Results
The median age of T1DM patients was 24.5 years [14-45]. The mean level of WBC was higher in T1DM patients with DKA than those without-DKA (11881.4$\pm$6971.36 vs 8191.3 $\pm$3210.36; P=0.21). T1DM patients with DKA had significantly higher serum NLR levels than those without DKA (9.71$\pm$ 8.85vs 2.30 $\pm$1.05; P=0.035). NLR was also significantly associated with the occurrence of DKA in T1DM patients (OR=2.18, 95%CI: 1.5–4.4, P=0.034). Furthermore, the levels of NLR were positively correlated with the circulating levels of creatinine (r=0.5; P=0.008) and negatively correlated with the circulating levels of albumin (r=-0.55; P=0.01). The mean level of PNR was significantly lower in patients with DKA than those without DKA (25.99 $\pm$14.96 vs 55.82 $\pm$20.77; P=0.001). The mean level of PLR was higher in patients with DKA than those without DKA (171.6 $\pm$93.54 vs 119.33$\pm$41.59; P=0.19). The ability of WBC, NLR, PLR and PNR in predicting DKA was analyzed using ROC curves. The most influential indicator for DKA patients was NLR (AUC 0.85; 95%CI: 0.7–1;p $<$0.005).The statistical threshold value of the NLR in predicting DKA was 2.05, with a sensitivity of 100% and a specificity of 50%.
Conclusion
Our findings indicate that the levels of WBC, NLR, and PLR were elevated in uninfected T1DM patients with DKA. The involvement of neutrophil-mediated inflammation may contribute to the pathogenesis of DKD in T1DM. Consequently, NLR can serve as a practical and cost-effective predictor for the occurrence of DKA in T1DM patients.
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EP240

Significance of Determining Inflammatory Markers and Carotid Artery Intima Media Thickness values in the Detection of Coronary Heart Disease in Asymptomatic Patients with Type 2 Diabetes
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Introduction
Increased levels of high-sensitivity C-reactive protein (hs-CRP) and interleukin 6 (IL-6) accelerates atherosclerosis and occurrence of cardiovascular complications in patients with type 2 diabetes (T2D). Intima-media thickness (IMT) is a surrogate marker of atherosclerosis in patients with T2D.
Aim
The aim of the study was to evaluate the significance of determining inflammatory markers IL-6, hs-CRP and IMT, as atherosclerosis markers, during a screening for presence of Coronary Heart Disease (CHD) in asymptomatic patients with T2D.
Methods
The study included 169 patients with T2D, without any symptoms and signs of CHD. Ergometric testing proved or ruled out the presence of CHD. Carotid ultrasonography was performed and IMT was measured. The levels of hs-CRP and IL-6 were determined by ELISA.
Results
Age, HbA1c, LDL cholesterol and albuminuria values were significant predictors of silent CHD ($P<0.05$). Other analysed risk factors: gender, smoking, duration of T2D, BMI, hypertension, total cholesterol and triglycerides did not show statistical significance in the prediction of CHD. It was proven that there was a greater possibility of the presence of silent CHD in asymptomatic patients with T2D with higher values of IMT($P<0.05$), IL-6 ($P<0.05$) and hs-CRP ($P<0.001$).Keywords: diabetes mellitus, coronary heart disease, inflammatory markers, intima-media complex

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EP241

Infection among type 2 diabetic hospitalized patients: A 4 year retrospective study

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Background and Aims
Acute and chronic infectious diseases appear to be more prevalent among patients having diabetes mellitus. Infections associated with diabetes could be particularly serious increasing morbimortality and treatment costs. Diabetic patients' predisposition to infections could be explained by the hyperglycemic environment impairing immune function. Other factors my contribute such as degenerative complications, for example autonomic neuropathy could decrease gastrointestinal and urinary motility.
Aim
The aim of this work is to assess the prevalence and type of infectious diseases among a type 2 diabetic hospitalized population.
Materials and Methods
We conducted a retrospective study including all type2 diabetics hospitalized in the Diabetology-Endocrinology department during the period 2018-2021.
Results
A total number of 357 type 2 diabetic patients was hospitalized during the study period. The average age was of 52.58 years [17-84]. A female predominance was noted (65.26%). Diabetic complications were distributed as following: 31.65% of patients had cardiovascular diseases, 33.05% a sensory polyneuritis, 29% a diabetic retinopathy, 10.92% a diabetic nephropathy and 8.68% an autonomic neuropathy. The prevalence of infections was of 26.61% with diabetic infected foot (8.96%) and urinary tract infection (7.5% of patients whose pyelonephritis in 85% of cases) as the main ones. Skin infections were present in 6.7% of cases of which the main was erysipelas (2.5% of all patients). Three patients had mycoses (0.8%) and a similar number had shingle. Measles, anthrax, furunculosis and skin wound infection were present in one case for each (0.44%). Respiratory infections affected 3.08% of patients: pneumonia was diagnosed in 1.96% and tracheobronchitis in 1.12% of the study population. Six patients (1.6%) had dental infections. Two patients (0.56%) had osteoarticular infections. A similar number of patients ($n=2$, 0.56%) had a digestive system infection. Regarding severity, a sepsis was noted in 3 cases (0.8%) (of which 2 urinary tract infections). Infection was the revealing factor of diabetes among 31.42% of the cases of recent diabetes.
Conclusion
Infection could be the first manifestation of diabetes mellitus, therefore patients consulting for acute infections and having risk factors for type 2 diabetes should be screened for hyperglycemia and for other metabolic features. Coexistence of diabetes and infection may precipitate metabolic acute complications, such as hypoglycemia, Ketosis, ketoacidosis and hyperosmolar states. Adopting a healthy life style and having a better glycemic control could reduce diabetes' morbidity including the related one to infections.

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EP242

Hand grip strength and risk of falls in adults with type 2 diabetes mellitus

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Objective
The objective of our study is to evaluate muscle strength and risk of falls in type 2 diabetes mellitus (DM2) patients
Methods
Observational cross-sectional study. Hand grip strength (HGS) (kg/cm^2) was measured with a Jamar. manual hydraulic dynamometer (5030j1; Jackson, MI).To classify normality, data from the Spanish population were used, establishing the cut-off point at p10. To assess the level of mobility and the risk of falls, the Time Up and Go(TUG) test was carried out. A score of less than 12 seconds was defined as low risk of falling and greater than 12 seconds as high risk of falling.
Results
The study included 60 patients with DM2 (60% men and 40% postmenopausal women). Mean age 66.3 ± 8.3 years. Body mass index (BMI) 30.8 ± 4.6. The mean values for dynamometry were 33.5 ± 22.5 kg in males and 21.5 ± 9.4 kg in women, being 96.6% below the 10th percentile. The prevalence of low muscle strength was analyzed by age group, quartiles of BMI and waist circumference (WC). We observed a progressive increase of low muscle strength with age .The prevalence of low hand grip strength was higher in the first and fourth quartiles of BMI and the fourth quartile of WC. According to the results obtained in the TUG test, 25% of men and 41.7% of women had a high risk of falls. Patients with high risk of falls showed significantly lower hand grip strength values than those with low risk of falls (13.8 ± 7.4 vs 18.7 ± 8.1; $P=0.027$).
Conclusions
HGS and TUG are practical tools for assessment muscle weakness in DM2 patients. Decrease in muscle strength should be recognized as a complication of DM2.

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EP243

Study on histomorphological features of the brain tissues in animals with experimental diabetes mellitus

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For quite a long time, the brain has been considered as an insulin independent organ capable of utilizing glucose without participation of insulin. Today, insulin is thought to be not only a regulator of glucose transport and metabolism, but also as a modulator of some processes, including neuronal excitability, proliferation and differentiation of progenitor cells, synaptic plasticity, memory formation, secreting of neurotransmitters and apoptosis. The work was initiated to comparatively analyze the morphological changes in the hippocampus of rats with experimental diabetes mellitus.
Materials and Methods
We studied the brain material taken from 7 rats with a diabetes mellitus model on a high-calorie diet and from 7 controls on the standard diet. Morphological studies were performed on the hematoxylin and eosin histologically stained specimens. The slices of the brain tissues prepared from the paraffin blocks in compliance with the standard methods were examined.
Results and Discussion
The trans-synaptic degeneration providing transfer of the damage from the damaged neuron to the normal one via a synaptic contact is the common process for neurodegenerative diseases of the central nervous system. Apoptosis is thought to be the main mechanism of the neuronal death taking place in neurodegenerative diseases. The findings from examination of the histological

specimens of tissues from rats with diabetes mellitus demonstrated pronounced atrophy of the nerve tissues as compared to those from the controls. Karyopycnosis of neurons could be seen in the cerebral cortex and in the hippocampus. In some places, neurofibrillary tangles could be seen in the cerebral cortex; there were perivascular edema, erythrostasis and a slight reduction in the neurons in the hippocampal region. In all regions under study, in rats with diabetes mellitus, the pronounced reduction of neurons as compared to the one in the controls could be seen. A reduction in the volume of the cytoplasm and nucleus, the membrane thickening and folding, moderate hyperchromatosis of the nucleus and the cytoplasm shrinking are the morphological signs evidencing the involvement of neurons in the apoptosis. Thus, the findings from the histomorphological studies demonstrated a reduction in the number of neurons and their karyopycnosis in the hippocampal region with the neurodegenerative damages, as well as changes in both composition of neurons and shape of the cell nuclei.

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EP244

Usability of early treatment intervention using personal continuous glucose monitor in hospitalized patients with type 2 diabetes

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It was reported that outpatients with type 1 diabetes using real-time continuous glucose monitoring (rtCGM) reduce HbA1c more than those using self-monitoring of blood glucose (SMBG). However, it is not well known whether inpatients with type 2 diabetes using rtCGM reduce glycemic variability more than those using SMBG. This is a prospective parallel-group comparative study. Sixteen patients with type 2 diabetes hospitalized for diabetes treatment were randomly allocated to 2 groups. In group 1, patients used personal continuous glucose monitor (CGM) [GUARDIAN CONNECT], and drug treatment intervention (DTI) is performed based on the sensor glucose levels (SG) in the rtCGM (CGM group). In group 2, patients used professional CGM (iPro2) and DTI is performed based on the capillary blood glucose levels (BG) measured using "glucometers for SMBG, that were compliant with ISO15197:2013 diagnostic test systems" ("GISO") [ACCU-CHEK Guide] (BGM group). In both groups, CGM was attached on the day of hospitalization (day 1) and used for 6 days. In group 1, all 288 SG were referenced for the intervention in real-time. In group 2, BG referenced for the intervention in real-time were measured at pre- and post- prandial time and bedtime (7 points) on days 2 and 5 and pre-prandial time and bedtime (4 points) on days 3 and 4. We preliminarily analyzed the 24-h SG measured using professional CGM (iPro2) for 150 patients with type 2 diabetes at our hospital to determine the target range for intervention using rtCGM to achieve both time-in-range (70–180 mg/dl) [TIR] $>$ 70% and coefficient of variation [CV] $<$ 36%. From this analysis, we determined the target range to achieve TIR $>$ 70% as "75–160 mg/dl" and that to achieve CV $<$ 36% as "within $\pm$30% of mean glucose levels". In both groups, DTI was performed at evening from day 2 to day 5 and morning from day 3 to day 5 based on the DTI algorithm unified for each CGM group and BGM group, where that determened target range was used. Two patients in the BGM group were excluded from this study because they could not carry out the research protocol (CGM group: $n=8$, BGM group: $n=6$). Patients in the CGM group achieved both TIR $>$ 70% and CV $<$ 36% earlier than those in the BGM group (1.4 days vs 2.7 days; $P=0.03$: Log-rank test). During hospitalization, the DTI with reference to rtCGM may achieve both TIR $>$ 70% and CV $<$ 36% slightly earlier than that with reference to BGM.

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EP245

Dynamics of C-peptide in patients with type 1 diabetes mellitus on the administration of Tolerogenic Dendritic Cells

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Introduction
Preserving of C-peptide secretion in type 1 diabetes mellitus (DM1) is an important goal in treatment, as it provides the possibility of optimal compensation. Various approaches are used to achieve this goal. We initiated a study to assess the potential effect of the cell therapy based on autologous Tolerogenic Dendritic Cells on the newly diagnosed DM1 (NCT05207995, ClinicalTrials.gov).
Methods
4 patients who were injected with Tolerogenic Dendritic Cells were given standard breakfast (carbohydrate content of 50 g). Fasting glycemia was determined in patients, the test was performed with fasting glycemia in the range of 3.8–9.0 mmol/l, short-acting insulin was not administered before breakfast. The test was carried out for 2 hours with the determination of the level of C-peptide at 0, 30, 60, 90 and 120 minutes. The levels of C-peptide after food stimulation were studied with the calculation of AUC (area under curve). Determination of the level of C-peptide is carried out by the method of chemiluminescent enzyme immunoassay on the analyzer Cobas E411 by Roche Diagnostics (Germany).
Results
There were no changes in insulin requirements (0.56 ± 0.16 U/kg vs 0.52 ± 0.18 U/kg during therapy), and basal levels of C-peptide (1.05 ± 0.55 ng/ml vs 1.36 ± 0.47 ng/ml during therapy) after the administration of Tolerogenic Dendritic Cells. When assessing stimulated levels of C-peptide, we detected an increase in AUC from 220.7 ± 111.9 ng/ml$\times$h. up to 317.6 ± 103.2 ng/ml$\times$h. Also, during continuous monitoring of glycemia, the time in the target range (TIR) reached the recommended value (more than 70%) and only in one patient the target level was not reached (TIR was 51%).
Conclusion
Short-term use of Tolerogenic Dendritic Cells is accompanied by an increase in the secretion of C-peptide in the process of food intake.

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EP246

The role and mechanism of peptide MSCP2 in regulating inflammation

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Mesenchymal stem cell (MSC), as a significant part of regenerative medicine, has been considered as a promising therapy in several diseases. Recently, the secretion effect of MSCs has been found to play a key role in the regulation of inflammatory. Here, we screened different peptides with high expression abundance by mass spectrometry from the supernatant of human umbilical cord MSCs. Also, we identified a peptide (AQTKRLVGDVLLATAFLSYSGP) named MSC-P2 derived from dynein axonemal heavy chain 5. Thus, we explored the role and potential mechanism of MSC-P2 in regulating inflammation of RAW 264.7 cells. ProtParam tool was used to analyze the physicochemical properties of MSC-P2. The instability index (II) of MSC-P2 is computed to be 20.50, classifying itself as a stable peptide. The aliphatic index is 110.91 and grand average of hydropathicity (GRAVY) is 0.441, proving its hydrophobicity. MSC-P2 entered into the cytoplasm of RAW 264.7 cells in 24 hours by fluorescence microscope. Cell Counting Kit-8 detection showed that MSC-P2 exerted no significant cytotoxicity at the concentration from 1uM to 100 uM. Besides, Real-time PCR showed that the mRNA expression levels of iNOS, TNF-α, and IL-6 were significantly down-regulated in the MSC-P2 group, compared with the control group ($P < 0.05$). Consistently, the protein expression levels of iNOS and TNF-α were significantly reduced in the MSC-P2 group, compared with the control group ($P < 0.05$) by Western blot and immunofluorescence. RNA transcriptome sequencing identified 2028 up-regulated genes and 1819 down-regulated genes in the MSC-P2 group ($|\log_2 FC| > 1$ and FDR < 0.05). KEEG analysis revealed that the down-regulated differentially expressed genes (DEGs) were mainly enriched in the pro-inflammation pathways including cytokine−cytokine receptor interaction, NF−kappa B signaling pathway, and NOD−like receptor signaling pathways. Besides, the up-regulated DEGs were mainly concentrated in metabolic pathways associated with anti-inflammation roles including fatty acid metabolism, biosynthesis of unsaturated fatty acids and PPAR signaling pathway. PPI network of top 30 DEGs was built by using the STRING database and it revealed 40 nodes and 92 edges. Most of these genes involving the network, such as Isg15, Fasn, Psmd11 and Tlr4, have been reported with the roles in the regulation of inflammation. This study will help us better understand the protective functions of the secretome from MSCs. In addition, it will provide an anti-inflammatory peptide, which will become a potential drug for prevention and treatment of inflammatory-related metabolic diseases.

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EP247

Intake of alpha-lipoic acid (thioctic acid) and insulin autoinmune syndrome. A case report

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A 52-year-old female patient with no previous history of interest, and with no prescribed habitual chronic treatment, was admitted to our hospital to be studied for symptomatic hypoglycemias of one month of evolution. Symptoms consisted of malaise, hunger, tremors and profuse sweating that disappeared with food ingestion. She referred hypoglycemic (up to 40 mg/dl) episodes daily, both in fasting and postprandial periods. She even suffered nocturnal episodes that woke her up. On physical examination the patient showed a good general condition, no abdominal masses were palpable, with neither acanthosis nigricans, abdominal obesity, nor lipodystrophic phenotype. Anthropometrically, she presented a waist circumference of 77 cm, a height of 154 cm, a weight of 54 kg and a BMI of 23. As for family history, one brother had been studied for postprandial hypoglycemia. On admission, blood tests showed a glycemia of 46 mg/dl with insulin 257 µIU/ml, proinsulin 5.3 pmol/l and beta-hydroxybutyrate 0.72 mg/dl. A mixed meal tolerance test was performed, showing hypoglycemia at 240 minutes of 53 mg/dl with insulin levels of 1012 µIU/ml and C-peptide of 1.62 ng/ml. Behind time, in a scheduled fasting test, no sugar levels below 45 mg/dl were evident. Research for hypoglycemic agents in urine was negative. The diagnosis of endogenous hyperinsulinism was therefore made and the study was completed with a thoracoabdominal CT scan and a somatostatin receptor scintigraphy where no focal lesions were observed. The study was completed with an echo endoscopy where two space-occupying lesions were evidenced in the pancreatic body which were punctured by FNA. In the pathological anatomy no neoplastic signs were evident. Positive anti-insulin antibodies were found (86.9% N 0-8.2). Hanging in there about previous treatments, the patient revealed a previous one month- treatment with a multivitamin that contained Lipoic Acid due to a meralgia paresthetica. HLA class II typing showed DRB1*04:03 and DRB1*15 alleles, commonly associated with Hirata disease. This is a common cause of hypoglycemia in Eastern ethnicities but extremely rare in Western populations. It is associated with drugs having a sulfhydryl group such as methimazole and lipoic acid among others. The patient was released with a diet distributed in 6 daily intakes, avoiding prolonged periods of fasting, and rich in complex carbohydrates. In addition, treatment with Diazoxide (50 mg/day) and Acarbose (75 mg/day) was started. These drugs where progressively decreased and in three months the patient gradually improved until all hypoglycemias disappeared.

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EP248

Predictive factors of obesity among adolescents in the governorate of Sousse, Tunisia

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Introduction
Obesity in youth has become increasingly common. This study aims to determine the predictive factors of obesity in adolescents.
Materials and Methods
This is an analytical cross-sectional study of a representative sample of high school students in the year 2019. Overweight and obesity were defined based on age- and sex-specific body mass index (BMI) z-score cutoffs. Data were analyzed using SPSS 20.0 software.
Results
A total of 1153 adolescents were recruited. The mean age was 17.19 ± 1.14 years with a minimum of 13 years and a maximum of 19 years. The sex-ratio M/F was 0.6. Obesity affected 9.4%, 95% CI [7.9%-11%] of adolescents. Regarding predictive factors, there was a female predominance (69.4%) in the obese group, whereas in the normal weight group, the female sex represented (59.4%), ($P=0.002$). Obesity was more common in adolescents with depression (68%) than in those without depression (31%) ($P<10\text{-}3$). We also noted that the majority (91%) of the obese used social networks versus (8%) who did not have access to these means ($P<10\text{-}3$). We found that (68%) of the obese did not engage in regular physical activity versus (31%) who did practice regular activity ($P=0.012$).
Conclusion
Normalization of body weight before the onset of puberty is very important because adolescents who are obese often maintain their weight until adulthood. In addition, obesity in adolescence is significantly associated with an increased risk of cardiovascular and metabolic diseases, such as type 2 diabetes, in adulthood. This study has identified some predictive factors of obesity in adolescents. The identification of these modifiable factors makes it possible to propose corrective actions to prevent the associated risk.

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EP249

Impact of maternal obesity on the course and outcome of pregnancies and breastfeeding

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Introduction
Obesity is a public health problem that also affects pregnant and breastfeeding women. Pre-gestational obesity is deleterious and can lead to several maternal and fetal complications, as well as a delay in the initiation of breastfeeding. The objective of this work is to evaluate the impact of maternal obesity on pregnancy, labor and the quality of breastfeeding.
Material and method
Prospective case-control study conducted at the endocrinology department of the UHC Ibn Rochd Casablanca. The study group included 50 obese parturients, and the control group 50 non-obese parturients. All our patients were followed for a diabetic pregnancy.
Results
The average age of our patients was 31 years (22-42), the average gestational age 27 SA (10-36). The average BMI was 36.2 kg/m^2, with an average pre-gestational BMI of 33.5 kg/m^2. The average weight gain during pregnancy was 15.3 kg. Gestational diabetes predominated at 58%, with 38% of DT2 and 4% of DT1. In the study group, gestational diabetes was diagnosed at the first trimester in 36% of patients. In the obese group, a higher rate of HTAG (42%; $P=0.004$), pre-eclampsia (12%; $P=0.004$), threats of premature delivery (14%, $P=0.005$) were observed., miscarriages and fetal deaths in utero (8%, $P=0.03$). Labor was obstructed in 12% of parturients ($P=0.001$), with a postpartum haemorrhage rate of 4% ($P=0.05$). A macrosomia rate of 24% was objectified in the obese group. Breastfeeding was initiated immediately postpartum in 72% of parturients, with an interruption of breastfeeding at 6 months in 44%. OGTT returned in favor of T2DM in 41.3% of patients whose diabetes was discovered during pregnancy.
Conclusion
Pre-gestational maternal obesity, as well as excessive weight gain during pregnancy, condition the course and outcome of pregnancy, with a higher rate of maternal-fetal complications, the risk of developing type 2 diabetes, as well as early termination of breastfeeding. Hence the importance of making obese patients aware of pre-gestational weight loss, with regular weight monitoring during pregnancy, in order to limit weight gain.

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EP250

Bilateral Cataracts in a Young Patient with Newly Diagnosed Diabetes: A unique Observation

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Introduction
Cataracts are an opacification of the crystalline lens, either partial or total, primarily caused by senescence, and rarely of metabolic origin. We present the case of a 24-year-old newly diagnosed with bilateral cataracts.
Case Presentation
E.S., a 24-year-old with newly discovered diabetes on insulin therapy, presented with a sudden and significant decrease in visual acuity. Ophthalmologic examination revealed bilateral cataracts with an inaccessible fundus. The patient was referred to us with an HBA1C of 13% for preoperative management.
Discussion
Diabetes is a metabolic disease that can have ophthalmic complications, particularly retinal and crystalline. Cataracts complicate diabetes in 8.8-22%. The pathophysiology of this cataract would be explained either by hyperglycemia leading to an elevation of glucose and its metabolites in the crystalline lens, the excess of intracellular glucose is unable to be metabolized by hexokinase, is converted into sorbitol and then into fructose. However, sorbitol and fructose do not cross the cell membrane, and accumulate, leading to intracellular hyperosmolarity or disruption of the function of the Na + K + ATPase pump, which can make the crystalline lens more sensitive to oxidative stress.
Conclusion
Cataracts are a rare complication of diabetes, especially in young people with newly diagnosed diabetes, which makes our observation unique.

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EP251

Newborns's condition and pregnancy outcomes in women with gestational diabetes

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Gestational diabetes mellitus (GDM) is a carbohydrate intolerance with onset or first recognition occurring during pregnancy. GDM could be risk factor for various maternal fetal complications.
Objective
To study newborns's condition to mothers with GDM and pregnancy outcomes in women with GDM.
Patients and methods
Obstetric and perinatal outcomes were compared in two mother-child groups. Group I consisted of 69 mothers with uncontrolled GSD and their 71 children, group II – 59 women with controlled GSD and 60 of their children. According to the existing criteria, blood plasma glucose values in pregnant women on an empty stomach/before meals/at night <5.1 mmol/l, and 1 hour after meals <7.0 mmol/l were considered normal.
Results
Mothers with uncontrolled GSD had statistically significant higher rates of pre-obesity and obesity before pregnancy (62.3% and 44.1% accordingly; $P<0.05$), chronic gynecological diseases (94.2% and 81.4% accordingly; $P<0.05$), preeclampsia (29.0% and 8.5% accordingly; $P<0.001$) and the threat of termination of pregnancy (40.6% and 20.3% accordingly; $P<0.05$) compared to women with controlled GSD. Group 1 newborns were statistically significant more likely to have complications and diseases of the early neonatal period (50.7% and 26.7% accordingly; $P<0.001$), macrosomia (25.4% and 11.7% accordingly; $P<0.05$), neonatal jaundice (12.7% and 1.7% accordingly; $P<0.05$), cerebral ischemia (46.5% and 23.3% accordingly; $P<0.001$), birth trauma (14.1% and 3.3% accordingly; $P<0.05$). Only children of group I had congenital malformations in 16.9% of cases. The incidence of diabetic fetopathy in group I newborns was almost 2 times higher, but without significant differences (12.7% and 6.7% accordingly, $p>0.05$). The presence of macrosomia and diabetic fetopathy in group II newborns may be associated with late diagnosis of GSD (after 30 weeks of gestation).Conclusion. A significantly higher frequency of adverse perinatal outcomes in newborns, as well as obesity, gynecological diseases and pregnancy complications in women with uncontrolled GSD compared to mothers with controlled GSD and their children was established. To normalize glycemic parameters in pregnant women with GDM and improve obstetric and perinatal outcomes, it is necessary to promptly prescribe rational insulin treatment schemes, if diet therapy is ineffective, and improve the quality of patient follow-up.

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EP252

Diabetes and survival in patients with squamous cell carcinoma of the upper aerodigestive tract

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Introduction
Type 2 diabetes is associated with an increased risk of cancer and with reduced survival in several types of cancer. However, data for upper aerodigestive tract carcinoma are limited.
Objective
Our aim of this report is to study the impact of diabetes on survival among patients with upper aerodigestive tract squamous cell carcinoma.
Material and Methods
A retrospective study of 130 patients treated for upper aerodigestive tract squamous cell carcinoma, between 1992 and 2019. Nasopharyngeal, nasal cavity and paranasal sinus carcinomas are excluded. We used the Kaplan–Meier method to calculate the cumulative proportion surviving. Survival curves were compared by log-rank test ($P<0.05$ for statistical significance). We used the Cox regression model for multivariate analysis.
Results
Our study included 117 men and 13 women. The mean age was 59 years. The tumor sites were: larynx (100 cases), hypopharynx (20 cases), tongue (9 cases) and lip (1 case). Twenty-nine patients (22.3%) had type 2 diabetes mellitus. No patient had type 1 diabetes mellitus. Five-year overall survival was 62.1% for nondiabetic group compared with 55.4% for diabetic group. There was no statistically significant difference between the 2 groups ($P=0.77$). Five-year disease-free survival was 60.8% for nondiabetic group compared with 54.7% for diabetic group, without significant difference ($P=0.63$). Multivariate analysis of overall and disease-free survival did not demonstrate a statistically significant difference between the diabetic and nondiabetic groups ($P=0.2$ for overall survival and $P=0.7$ for disease-free survival).
Conclusion
The impact of diabetes on survival in upper aerodigestive tract squamous cell carcinoma is controversial in the literature. Our results demonstrate that there is not a difference statistically significant in overall or disease-free survival among non-diabetic and type 2 diabetes mellitus patients.

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EP253

Quality of life in patients with severe complications of diabetic foot syndrome with chronic kidney disease

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Aim
To evaluate the effect of the terminal stage of CKD on the quality of life (Qol) associated with health in patients with DFS.
Material and Methods
48 patients were examined with DM 2 in the period 2021 -2022 .All observed patients were divided into 2 groups: 1 gr. - 23 patients with DFS, complicated by ulcers, gangrene and amputation and combined with CKD 4-5 stages on hemodialysis. 2 gr - 25 patients with DFS, complicated by gangrene and amputation, without CKD. The control group amounted to 20 healthy persons. The patients were performed biochemical (bilirubin, straight, indirect, lipid spectrum, Alt, Ast, Coagulogram, blood sugar, glycated hemoglobin, urea, creatinine, and instrumental: ECG, MRI of foot, etc. The quality of life was evaluated using the international questionnaire a brief form SF-36.
Results
Both groups consisted of patients with an active form of diabetic foot (ulcer, stacker stop, infection) and were comparable by age and sex. It was found that patients with DFS and tsCKD on hemodialysis have significantly higher levels of creatinine, lower levels of hemoglobin, lower levels of albumin, higher performance of peripheral arteries, and lower neuroarthropathy rates of Charcot than in patients with DFS without tsCKD. In patients with DFS with tsCKD on hemodialysis there is a decrease in the quality of life, manifested by low indicators of both physical (by 49.3%) and psychological (by 50.1%) health components. Patients with DFS without tsCKD have a decrease in the of Qol., manifested by low indicators of both physical (by 27.8%) and psychological (by 34.6%) health components
Conclusions
tsCKD negatively affects physical quality of life to a greater extent than mental, in patients with DFS. 2).

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EP254

Quality of life in patients with diabetic neurogenic bladder

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Background and Aim
Diabetic neurogenic bladder (DNB) is a frequent complication affecting up to 45% of patients suffering from diabetes mellitus (DM). Our study aims to evaluate the impact of DNB on the quality of life (QoL) in this population.
Patients and Methods
We conducted a descriptive cross-sectional study involving 200 patients with DNB. Their QoL was assessed using the Ditrovie scale.
Results
The mean age was 59.3 ± 10.6 years with a female predominance (55.5%). The average duration of diabetes was 11 ± 7.9 years. Mixed insulin-oral antidiabetic treatment (44.2%) was most often proposed. A glycaemic imbalance was noted in 79.7% of patients with a mean HbA1C of 9.2 ± 2.4%. Microvascular complications related to diabetes were frequent: retinopathy (29.6%), nephropathy (9.5%), and sensory-motor neuropathy (53.5%). Macroangiopathy was reported in 21.6%. Overactive bladder (70.5%) was the most reported urinary

disorder, followed by dysuria (51.5%) and stress urinary incontinence (22.5%). The mean Ditrovie score in our series was 2.52 (range = 1-5). QoL was impaired in 44% of patients who described their experience as "bad" (9.5%), "average" (13%), or "worse" (21.5%). Only 18.2% of the surveyed patients had received consultations for their urinary discomfort. Less than 5% were cured or satisfied with the management.

Discussion

DNB is an autonomous complication that is largely underestimated in clinical practice. Patients presenting DM do not report symptoms unless the urinary discomfort would have a severe impact on daily activities. Thus, screening for these disorders should be done systematically by healthcare providers during diabetes consultations.

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EP255

Dietary and metabolic factors predictive of pancreatitis occurrence in type 1 diabetes

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Objective

to analyze the dietary and metabolic factors predictive of the occurrence of pancreatitis in patients with type 1 diabetes mellitus (T1DM).

Patients and Methods

Analytical case-control study of 31 T1DM patients separated into two subgroups: G1 ($n = 10$): T1DM cases with pancreatitis. G2 ($n = 21$): T1DM controls without pancreatitis.

Results

The age at diagnosis of T1DM was comparable between the two groups. A discrete female predominance was noted in G1 (60% vs 38.1%; $p > 0.05$). The mean BMI was higher in G2 (20.7 ± 3.7 vs 22.9 ± 4.2 kg/m^2; $P = 0.839$). Controls had more android fat distribution (25% vs 14.3%; $P > 0.05$). G1 T1DM had a higher calorie diet than G2 (2838.8 ± 889.4 vs 2777.8 ± 872.8 kcal/d; $p > 0.05$) with higher intake of simple sugars (42.33 ± 24.1 vs 33.5 ± 35.2 g/d), calcium (558.3 ± 177.7 vs 519.6 ± 226.6 mg/d) but lower fibre (13.7 ± 3.9 vs 17 ± 6.3 g/d). The markers were similar except for phosphorus, which was significantly higher in G1 (1.13 ± 0.41 vs 1 ± 0.23 mmol/l); $P = 0.037$)The dietary and metabolic factors aggravating the risk of pancreatitis in T1DM were associated with dyslipidemia (OR = 3.3; $P = 0.000$), the presence of a metabolic syndrome (OR = 8.14; $P = 0.000$), pre-existing microangiopathy (OR = 3.84; $P = 0.013$) and iterative diabetic keto-acidosis (OR = 2.96; $P = 0.049$).

Discussion

Prevention and treatment of dyslipidemia and metabolic syndrome are key to reducing the risk of pancreatitis in T1DM. Dietary management and physical activity remain the most effective.

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EP256

Influence of diabetes mellitus on changes in preperitoneal fat measured by nutritional ultrasound, in a cohort of patients who required intensive care unit (ICU) admittance due to severe covid-19 pneumonia, during a 6-month follow-up program

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Introduction and Objectives

Preperitoneal fat is an ectopic visceral adipose tissue with a significant proinflammatory metabolic impact. The objective of this study is to measure preperitoneal fat by nutritional ultrasound at discharge, 3 months and 6 months in a cohort of patients who required admission to the Intensive Care Unit (ICU) due to severe COVID-19 pneumonia, and to analyze the differences based on the presence or not of previous DM.

Material and Method

Complete morphofunctional assessment was performed on 76 patients who were admitted to the ICU due to severe COVID-19 pneumonia, at discharge, 3 months and 6 months. Subsequently, preperitoneal fat measured by nutritional ultrasound was compared between diabetic and non-diabetic patients, using ANOVA for paired data (corrected by the Bonferroni test).

Results

Prospective observational study including 76 patients, 22 diabetics and 54 non-diabetics.

Conclusion

During follow-up, patients without diabetes present a statistically significant decrease in preperitoneal fat, probably related to the resolution of the intercurrent infection (decrease in CRP during follow-up). In contrast, in diabetic patients it remains constant with no differences during follow-up despite the progressive decrease in CRP, which may be related to the chronic metabolic impact produced by DM.

Table 1 Severity of Acute COVID-19 by Serum Glucose Levels and BMI

	Baseline	3 months	6 months	Global *P* (a,b,c)
Preperitoneal fat (non-DM) (cm)	0.856(0.5)	0.671(0.5)	0.469(0.3)	**0.011**(0.056,0.09-2,1.000)
Preperitoneal fat (DM) (cm)	0.503(0.3)	0.469(0.3)	0.538(0.4)	0.859(0.848,0.97-5,1.000)

a = statistical significance baseline-3 months ($P < 0.05$).
b = statistical significance baseline-6 months ($P < 0.05$).
c = statistical significance 3 months-6 months ($P < 0.05$).

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EP257

Hyperhomocysteinemia in type 2 diabetes, a risk factor for the complications of diabetes?

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Introduction

Patients with type 2 diabetes mellitus are considered at least at high cardiovascular risk. Cardiovascular risk factors must be regularly screened. Hyperhomocysteinemia is considered as an independent risk factor for atherosclerotic disease and coronary disease in some studies. The aim of our study was to confirm the association between hyperhomocysteinemia and atherosclerotic disease in patients with type 2 diabetes.

Methods

We performed a cross-sectional study including 257 type 2 diabetes mellitus patients. For each patient, we looked for personal history of high blood pressure, the duration of diabetes, its treatment and its complications. HbA1c and homocysteine were measured. Hyperhomocysteinemia was diagnosed when homocystein levels were above 15 µmol/l.

Results

The mean age was 59.8 ± 8 years, with extremes ranging from 32 to 84 years old. Mean duration of diabetes was 10.4 ± 5.3 years, with extremes ranging from 3 to 27 years. Hypertension was present and treated in 61.1% of the patients. Mean HbA1c was 8.7 ± 1.9% with extremes ranging from 5.6% to 15.7%. A macrovascular complication was present in 21.8% of cases, with a coronary disease in 17.9%, a cerebrovascular accident in 5.1% and a peripheral artery disease in 1.9% of cases. A microvascular complication was present in 79.4% of cases, with retinopathy in 23.7%, a nephropathy in 31.2%, and a peripheral neuropathy in 54.5% of cases. Mean homocysteine level was 13.3 ± 5.2µmol/l. A hyperhomocysteinemia was found in 26.5% of patients. Hyperhomocysteinemia

was positively associated with age ($P=0.001$), male gender ($P=0.001$), the presence of a macrovascular complication ($P=0.002$), and of a cerebrovascular accident ($P=0.046$). High blood pressure, coronary disease, peripheral artery disease, retinopathy, nephropathy, peripheral neuropathy and HbA1c level were not associated with hyperhomocysteinemia.
Conclusion
Hyperhomocysteinemia is frequent in type 2 diabetic patients. The association between hyperhomocysteinemia and macrovascular complications in particular cerebrovascular disease makes us consider the impact of homocystein levels on the onset of cardiovascular disease and how it consists as a risk factor to monitor.

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EP258

Advanced glycation end products association in patients with diabetes mellitus

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Introduction
Advanced glycation endproducts (AGEs) are sugar-modified products that arise during the non-enzymatic glucose oxidation process. AGEs promote oxidative stress and are associated with poor diabetes mellitus (DM) control, metabolic syndrome, and cardiovascular disease.
Objective
to evaluate AGEs accumulation in the diabetic patients' skin and its relationship with DM type, disease duration, and complications.
Methods
116 patients (19-85 years, 66 females and 50 males) with type 2 (T2DM) and type 1 (T1DM) DM, were enrolled in the study during the 2022 year. AGEs were measured non-invasively using an AGE Reader device (DiagnOptics Technologies B.V., SN 00010604, The Netherlands). Patients filled out questionnaires about diabetes and data on diabetes type, duration, and control were collected from medical records. Patients were divided into groups according to: DM types, disease duration (<15 ($n=61$) and ≥ 15 ($n=54$) years), microvascular DM complications (with ≥ 1 microvascular complication ($n=72$) and without ($n=43$)), macrovascular DM complications (with ≥ 1 complication ($n=24$) and without ($n=92$)).
Results
50 T1DM (30 females and 20 males; age 40 ± 12.4 SD years; DM duration 18.8 ± 0.495 SD years) and 60 T2DM (36 females and 30 males; age 63.4 ± 9.4 SD years; DM duration 11.6 ± 8.4 SD years) participated in the study. A significantly higher mean AGEs concentration was found in T2DM vs T1DM patient group (2.4 ± 0.4 SD vs 2.2 ± 0.5 SD, respectively, $P=0.011$). Also, higher mean levels of AGEs were found in patients with longer duration of DM (≥ 15 years) (2.2 ± 0.4 SD vs 2.4 ± 0.4 SD, respectively, $P=0.047$). No significant difference in AGEs concentration between the groups of patients with and without microvascular complications was found (2.4 ± 0.5 SD vs 2.3 ± 0.4, $P=0.327$). However, a higher mean concentration of AGEs was observed in the group of patients with macrovascular DM complications (2.6 ± 0.4 SD vs 2.3 ± 0.4 SD, respectively, $P=0.002$).
Conclusion
A significantly higher AGEs accumulation was found in patients with T2DM, those with macrovascular complications, and longer than 15 years of disease duration. The presence of microvascular complications was not related to concentration.
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EP259

COVID-19 infection in lipodystrophy syndromes

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Purpose
The coronavirus disease 2019 (COVID-19) has a high morbidity and mortality in patients with chronic disorders. This study was aimed at assessing the frequency and outcomes of COVID-19 in patients with lipodystrophy syndrome and investigating the effect of restricted access to the hospital during pandemic on metabolic parameters.
Methods
A survey comprising descriptive questions about the situation of the patients during the COVID-19 pandemic was created and performed by a phone call. Patients were asked if they had COVID-19 so far; if so, the hospitalisation, the need for intensive care and the oxygen requirement, COVID-19 treatment and ongoing findings after COVID-19 infection were questioned. Laboratory data from hospital records were retrospectively analysed, and the results after the COVID-19 period, if any, were obtained from the patients.
Results
A total of 71 patients were included. Patients with lipodystrophy had at least one comorbid disease; diabetes mellitus was the most common (87.1%). Six patients (8.5%) stated that they had COVID-19 infection, of which three were hospitalised and one was followed up in the intensive care unit. No death was reported. Microalbuminuria was significantly worsened in all patients compared to their pre-pandemic status.
Conclusions
Patients with lipodystrophy have a high risk of severe COVID-19 due to their multiple comorbidities. Further studies with larger patient groups are needed to verify these findings. Metabolic parameters of patients with rare diseases were deteriorated during the pandemic.

The course of COVID-19 in lipodystrophic patients

	Yes, *n* (%)	No, *n* (%)
Hospitalisation	3(50)	3 (50)
Intensive care unit	1 (16.7)	5 (83.3)
Oxygen support	2 (33.3)	4 (66.7)

Abbreviations: COVID-19, coronavirus disease 2019.

Comparison of metabolic parameters during the pandemic period with the pre-pandemic period

	Pre-pandemic period (Mean ± SD)	Pandemic period (Mean ± SD)	*P*
HbA1c (%)	7.08 ± 1.69	7.29 ± 1.82	0.741
Spot Urine microalbumin (mg/dl)	311.61 ± 1050.32	371.52 ± 749.84	**0.013**
TC (mg/dl)	186.09 ± 72.68	178.91 ± 84.35	0.545
LDL cholesterol (mg/dl)	98.36 ± 71.50	92.00 ± 52.67	0.451
HDL cholesterol (mg/dl)	40.05 ± 23.04	36.53 ± 15.48	0.593
TG (mg/dl)	340.81 ± 392.77	379.83 ± 687.51	0.379

Abbreviations: SD, standard deviation; HbA1c, glycated haemoglobin; TC, total cholesterol; LDL, low-density lipoprotein; TG, triglycerides; HDL, high-density lipoprotein.

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EP260

Relation of HLA system genes in patients with type 1 diabetes and other autoimmune diseases

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Background
Type 1 diabetes mellitus (T1DM) is caused by destruction of pancreatic beta cells. Children and adolescents with type 1 diabetes have an increased risk of developing other autoimmune diseases, most commonly autoimmune thyroiditis and celiac disease.
Objectives
To examine the frequency of individual human leukocyte antigen (HLA) alleles in people with T1DM and associated autoimmune (AI) diseases of the thyroid, digestive system, and skin, and to examine differences in gender and age at the time of diagnosis.
Subjects and Methods
Subjects were patients referred to the Clinical Institute of Transfusion Medicine for HLA typing. Data were collected in Clinical hospital center Osijek (HLA typing findings, associated autoimmune diseases of the thyroid gland, digestive system, and skin; age and sex).
Results
The study was conducted on 147 subjects with T1DM (51.7% women, 48.3% men). The AI disease of thyroid were most common (24.5%). Distribution of subjects by age groups differs significantly. The most common HLA alleles in men are HLA-DRB1*03, -DQA1*05, -DQB1*02, and in women HLA-DRB1*03, -DQA1*03, -DQB1*03(DQ8). Subjects with T1DM were more likely to have the DRB1*03-DQA1*05-DQB1*02 haplotype, and female subjects with T1DM were more likely to have the DRB1*08-DQA1*03-DQB1*03(DQ8) haplotype. There is a significant difference in the distribution of subjects with respect to the presence of autoimmune AI thyroid disease vs HLA-DRB1*03/*10,-DRB1*03(DQ8); AI of the digestive system disease relative to HLA-DRB1*01; AI skin disease versus HLA-DRB1*01, -DQB1*05.
Conclusion
Age is associated with an earlier diagnosis of T1DM, while gender is not. Individual HLA alleles have been associated with the earlier onset of T1DM and AI disease. The incidence of T1DM in the population is increasing and a proper understanding of the mechanism of occurrence is crucial to better diagnose and prevent the development of complications.
Keywords: diabetes mellitus, type 1; histocompatibility antigens class II; autoimmune diseases

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EP261

Features of the GCK-MODY and HNF1A-MODY: Dynamic observation data

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Diabetes mellitus (DM) type MODY (Maturity Onset Diabetes of the Young) accounts 10% of cases of diabetes with onset before 35 years. The aim was to determine characteristics of the course of the main types of MODY.
Materials and Methods
45 patients aged 18 to 35 years diagnosed with MODY molecular genetic testing (next-generation sequencing technology and direct automated Sanger sequencing) were included: 31 had mutations in the *GCK* gene, 14 - in the *HNF1A* gene, they were under dynamic observation for three years. All patients had at baseline and after three years: clinical examination, biochemical blood test, determination of HbA1c, C-peptide, thyroid status, microalbuminuria. Statistical processing of the results was done using the SPSS 20 program.
Results
The median age of patients with GCK-MODY was 21.5 [18.3; 34.6] years, HNF1A-MODY – 24.4 [19.8; 34.8] years ($P=0.108$). The majority of patients (87.1% and 96.8%) ($P=0.562$) with GCK-MODY had no symptoms of hyperglycemia at baseline and after three years. Hypercholesterolemia (25.8%) and allergic reactions (22.6%) prevailed among comorbidities. Patients with GCK-MODY had normal level of median C-peptide - 0.9 [0.6; 1.1] ng / ml at baseline; 0.8 [0.6; 1.9] ng/ml at 3 years ($P=0.864$), HbA1c targets were achieved (median 6.3 [6.0; 6.9]%; 6.5 [6.1; 7.0]% - after three years ($P=0.130$)). 48.4% achieve normoglycemia with a diet. 57.1% with HNF1A-MODY had symptoms of hyperglycemia at baseline and 14.2% ($P=0.062$) after three years. Hypercholesterolemia (64.3% at baseline; 46.2% after three years) ($P=0.180$) and arterial hypertension (28.6% at baseline and after three years) ($P=1.000$) prevailed among comorbidities. Median of C-peptide - 0.8 [0.6; 1.0] ng / ml at baseline; after three years - 0.6 [0.5; 1.0] ng/ml ($P=0.840$)) was normal; HbA1c levels increased slightly (7.0 [6.6; 7.6]% and 7.2 [6.7; 7.5]% ($P=0.102$)). Most patients achieve normoglycemia with oral antihyperglycemic therapy (42.9% at baseline, 50.0% at three years) ($P=0.668$)).
Conclusions
1. Majority patients with GCK-MODY had an asymptomatic course of the disease with moderate, non-progressive fasting hyperglycemia.2. Majority patients with HNF1A-MODY had stable indicators of carbohydrate metabolism remained during dynamic monitoring but they had poorly metabolic control in comparison with GCK-MODY.Acknowledgements: Abstract was written of the grant of the President of the Russia for state support of young Russian scientists - doctors of sciences MD-3017.2022.3.

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EP262

Diabetic health literacy and its association with medication adherence among adult patients with type 2 diabetes mellitus

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Introduction
Poor adherence to prescribed diabetic medication is a major contributor to disparities in effective glycemic control among patients with type 2 diabetes mellitus. The purpose of this study was to investigate the association between health literacy level and adherence to diabetic medications among this population.
Methods
A cross-sectional survey enrolled 66 patients medically treated for type 2 diabetes mellitus. Patients with dementia syndromes or impaired cognition were excluded. diabetic medication adherence and health literacy were evaluated respectively by the 6-item Morisky Medication Adherence Scale and the 16-items European Health Literacy Survey Questionnaire (HLS-EU-Q16). Socio-demographic characteristics were assessed during the consultation.
Results
The mean age of patients was 63.35 ± 12.63 years. Adherence scores ranged from 0 to 6 with a mean score of 2 ± 1. Overall, only 16.7% of participants had good adherence levels to diabetic medications. The mean score on the literacy questionnaire was 7 ± 3. Adequate health literacy was associated with a higher adherence score ($P=0.001$) and better glycemic control ($P=0.03$). Internet was reported to be the preferred source of health information by 60% of participants with adequate health literacy. All the participants with inadequate health literacy answered wrong about the doctor's comprehension questions. The low educational level ($P=0.041$), lack of medical and social security ($P<0.01$), and low socioeconomic levels ($P<0.01$) were correlated with inadequate health literacy.
Discussion
In this study, no correlation was found between male sex and adequate health literacy, this finding is different from previous research studies and may be explained by the limited variability in health literacy scores among study participants and the limited number of the population. However, the straight of our study that it is one of the rare studies in our country investigating the association between health literacy and diabetic medication adherence among patients with type 2 diabetes mellitus.
Conclusion
Tailored interventions considering health literacy are needed to support medication adherence in order to improve glycemic outcomes of patients with type 2 diabetes mellitus. Additional studies are needed to identify and prioritize factors targeting an effective adherence intervention for this population.

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EP263

Insulin resistance in the course of acne

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Introduction
Acne vulgaris is a common skin disorder among both adolescents and adults. Its multifactorial pathogenesis may include insulin resistance, especially in cases resistant to classical treatment methods. There are few studies which have already

proved acne vulgaris development in the course of insulin resistance, however, there are more studies necessary in order to include insulin resistance evaluation in classical acne vulgaris diagnosing and treatment.
Objective
To investigate acne vulgaris development in the course of insulin resistance.
Material and Methods
41 acne vulgaris patients and 47 healthy age and BMI-matched controls were involved in the study. Glucose and insulin fasting serum levels were obtained from each participant, later HOMA-IR was calculated and insulin resistance was diagnosed in cases with HOMA-IR value over 2.1.
Results
The mean ± SD glucose fasting serum level was 94.88 ± 7.731 [mg/dl] in study group and 79.51 ± 7.175 [mg/dl] in control group ($P < 0.001$). The mean insulin fasting serum level was 14.47 ± 6.394 [μIU/ml] in study group and 11.83 ± 4.309 [μIU/ml] in control group ($P = 0.059$). Calculated HOMA-IR mean value in study group was 3.4 ± 1.49 and in control group 2.34 ± 0.909 ($P < 0.001$).Out of 41 patients 32 were diagnosed with insulin resistance (78%) and out of 47 controls 26 were diagnosed with IR (55%) ($P = 0.026$).
Conclusions
HOMA-IR values were found to be statistically higher in acne patients compared to healthy controls. Insulin resistance diagnosis was statistically more common among the group of acne patients compared to controls. Insulin resistance might be an independent factor in acne vulgaris development and should be considered in the process of acne diagnosing and treatment.

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EP264

Prevalence and factors associated with hypoglycaemia in type 1 diabetes

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Introduction
Hypoglycaemia is the most common metabolic complication in type 1 diabetes. Although rarely dangerous, it significantly impairs quality of life. The aim of our study was to determine the prevalence and factors associated with hypoglycaemia in T1DM.
Methods
Descriptive cross-sectional study conducted over 3 months in ward C of the Institute of Nutrition, which included patients with type 1 diabetes.
Results
Fifty-seven patients were included, of whom 31 were women and 26 men. The characteristics of the patients were respectively: age: 32.3 ± 9.6 years, BMI: 23.16 ± 3.1 kg/m^2, HbA1c: 10 ± 2.2%, duration of diabetes: 16.1 ± 8.8 years, duration of insulin therapy > 10 years: 65%. Forty-two patients were on human insulin and 15 patients on insulin analogues. Of these, 78% were on basal/bolus plus. 72% of our patients had at least one episode of hypoglycaemia in the previous 6 months. The frequency of hypoglycaemia was correlated with the length of time the patient had diabetes ($P = 0.02$), the number of insulin injections per day ($P = 0.013$) and with gender, with women having more hypoglycaemia than men ($P = 0.028$). Moreover, the higher the frequency of hypoglycaemia, the higher the HBA1C ($P = 0.031$). However, there was no statistically significant correlation between the prevalence of hypoglycaemia and chronic degenerative complications of diabetes.
Conclusion
In T1DM patients, the predictive factors for hypoglycaemia are: female gender, duration of diabetes, duration of insulin treatment and number of injections.

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EP265

Mauriac syndrome: A case report

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Introduction
Mauriac syndrome is typically characterised by poor glycaemic control in type 1 diabetics. It is associated with diabetes, hepatomegaly, disturbed liver function and severe staturo-weight delay.
Observation
We report the case of a young type 1 diabetic patient referred to our department for further management of a glycaemic imbalance. The patient was 16 years old, type 1 diabetic for 10 years on insulin analogues, with a history of vitiligo since the age of 5 years, febrile convulsion at the age of 3 years, put on valproic acid for 2 years. The clinical examination showed a delay in growth and development and puberty (< 4 DS, Tanner stage 1), hepatomegaly with a liver arrow at 17 cm. The biological work-up showed an HbA1c of 11%, hepatic cytolysis at 3 times normal with negative hepatitis B and C serology. A strictly normal hormonal work-up including FSH, LH, testosteronemia, cortisol and GH with normal GH stimulation test. Celiac disease serology was negative with no villous atrophy on oesogastroduodenal fibroscopy. Abdominal CT scan showed homogeneous hepatomegaly with regular liver contours. Based on these clinical, biological and radiological arguments, Mauriac syndrome was strongly suspected, hence the indication for a liver biopsy, which was refused by the patient.
Conclusion
Our observation illustrates the importance of evoking Mauriac's syndrome when hepatomegaly with statural delay is discovered in a type 1 diabetic. The diagnosis of certainty is histological and the treatment is based on the control of diabetes.

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EP266

The clinical and biological factors associated with the use of insulin therapy in women with gestational diabetes

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Objective
The objective of our study was to identify maternal and biological factors associated with the use of insulin therapy in patients with GDM.
Methods
Retrospective study including 100 pregnant women followed up for gestational diabetes during the year 2021. Information was collected from medical records and supplemented, if necessary, by telephone interviews with the patients.
Results
The mean age of the patients was 32.7 ± 4years. Half of the population had a first-degree family history of type 2 diabetes and 52% were obese with a mean body mass index of 29 ± 5.5 kg/m^2. The mean gestational age at discovery of GDM was 19.4 ± 7SA. The diagnosis was made on the basis of pathological fasting blood glucose in 67% of cases. Insulin therapy was indicated in 32% of cases. Compared to pregnant women with diabetes controlled by dietary measures alone, insulin-treated patients had higher gestational age and parity, earlier gestational age at discovery of GDM and more frequently had two pathological oral glucose values, but the difference was not significant. In multivariate analysis, the factors significantly associated with the use of insulin therapy were the existence of a first-degree family history of type 2 diabetes, pre-gestational obesity and an HbA1c ≥ 5.5% at the discovery of GDM.
Conclusion
Knowledge of the factors associated with insulin therapy helps to optimise the management of gestational diabetes and thus improve the maternal-fetal prognosis.

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EP267

Comparison of cardioprotective effects of empagliflozin and vildagliptin

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Background and Aim
To study the cardioprotective effects of empagliflozin and vildagliptin in patients with diabetes type 2.
Method
90 patients with type 2 diabetes were randomized using a random number generator into 3 groups, depending on the antihyperglycemic therapy prescribed for the next 6 months: the group that continued to receive gliclazide and metformin, the group in addition to gliclazide and metformin received vildagliptin at a dose of 100 mg/day, the group in addition to gliclazide and metformin received empaglilflozin at a dose of 25 mg/day.

Results
Empagliflozin therapy was accompanied by regression of the left ventricular mass index (118.00 [116.00; 121.00] g/m^2) vs 121.00 [118.00; 122.00] g/m^2) and a decrease of the natriuretic peptide (proBNP) (23.50 [16.70; 33.30] pg/ml vs 31.00 [24.30; 46.20] pg/ml ($p < 0.05$).
Conclusion
SGLT2 inhibition by empagliflozin has a complex and multifunctional effect on the body that can effectively influence cardiovascular outcomes.

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EP268

Experience of the transition from pediatrics to adult medicine by young type 1 diabetics

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Introduction
Type 1 diabetes (T1D) is the most common metabolic disease in children and adolescents. The transition of care from pediatrics to adult medicine is a real challenge and can be experienced by patients as a huge struggle.
Objective
The objective of this work is to retrospectively study the experience of transition by young type 1 diabetics, in order to shed light on the factors facilitating or hindering this transition.
Materials and Methods
Retrospective study conducted in the endocrinology and diabetology department of the UHC Ibn Rochd, including 60 T1D patients followed in the young adult consultation, referred from the pediatric diabetology department of Harouchi hospital. These patients answered a questionnaire concerning their experience of this transition.
Result
The average age of our patients was 16 years (14-20), with a female predominance (60%), all were on a basal bolus regimen. The average age of diagnosis of diabetes was 7 years. The average age of transition was 14 years old. The announcement of the transition was made by the pediatrician in all our patients. Regarding the feelings of patients at the time of the announcement, 41.6% were curious, 45% worried, 5% refused the transition, and 8.3% had no opinion. The average HbA1c at the time of transition was 8%. At the first young adult consultation, 70% of patients were accompanied by their mother, 25% by their father, 5% came alone. The establishment of trust with the healthcare team was rapid in 60% of patients. The first hospitalization in adult medicine was for diabetic ketosis in 66% of patients (including 70% on insulin withdrawal), severe hypoglycemia in 5%, and for glycemic imbalance in 29%. The average time between the transition and the first hospitalization was 6 months. Regarding the overall experience of the transition in our patients, it was easy and smooth in 40%, difficult in 45%, while 15% did not realize it.
Conclusion
The transition from pediatrics to adult medicine is a critical period for young people with T1D which can be difficult for some, thus causing a glycemic imbalance, or even acute decompensation of their diabetes. Hence the importance of being aware of the factors hindering this transition in order to make it easier, especially during adolescence.

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EP269

Pseudohyponatremia caused by hyertriglyceridemia: A case report

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Introduction
Serum sodium assay is one of the most commonly performed laboratory tests in a hospital setting. However, in some instances, the reported laboratory sodium results may not reflect the true actual values. Overcorrection of the serum sodium levels in pseudohyponatremia may cause serious complications
Case Presentation
A 31-year-old woman was hospitalized in June 2022 in endocrinology department for asymptomatic hyponatremia. She was followed in endocrinology department since 2014 for hypertriglyceridemia (Familial hyperlipoproteinemia type 4). She has a history of type 1 diabetes treated withi nsulin since 2009 and 3 episodes of acute pancreatitis (type D and E), the last one was in December 2015. Results of Biochemical parameters at admission were as follows: sodium 124 mmol/l, potassium 3.7 mmol/l, chloride 98 mmol/l, triglyceride 20 mmol/l, cholesterol 4.3 mmol/l, glycemia 3.5 mmol/l.His laboratory results obtained with AU 480® Beckman Coulter. Given the high triglyceride level in the sample as a potential cause of pseudohyponatremia, we used a direct ISE (electrode selective of ions) method on ABL80® Radiometer to check sodium concentration and obtained a result of 139 mmol/l in a sample with a sodium of 124 mmol/l by the indirect ISE on AU 480® Beckman Coulter.
Conclusion
Pseudohyponatremia is a measurement artifact when the fraction of solid-phase particles is more than the physiological range like in hyperlipidemia.Clinicians must be aware about the methods involved in the measurement to prevent mismanagement in such conditions. Direct ISE may be an alternate option in these conditions.

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EP270

Ultrasonographic features of thyroid nodules and thyroid gland in obese patients

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Objective
Thyroid nodules are one of the most common thyroid diseases. Ultrasonography is an reliable and the most commonly used imaging method in the evaluation of thyroid nodules with a high sensitivity (Sn) and specificity (Sp). The prevelance of obesity, especially severe obesity, is increasing at an alarming rate in the worldwide. Although obesity and thyroid disorders are related to each other, the pathological relationship between those is not clear. Several studies have revealed that thyroid nodules are associated with adiposity which is assessed by body mass index (BMI). In this study we aimed to evaluate the morphological structure of the thyroid gland and thyroid nodules in obese patients according to the degree of the obesity.
Methods
273 patients with BMI>30 kg/m^2 and applied to our endocrinology outpatient clinic between 2019 and 2022 years for obesity or any other reason and also requested thyroid ultrasonography and thyroid function tests were analyzed retrospectively. The demographic data of the patients (sex, age), thyroid function tests, thyroid ultrasonography features (thyroid gland size, volume, parenchyma structure, and, if any, nodule and nodule features) and also if there is thyroid nodule cytology, were evaluated. According the body mass index patients were divided as class I (BMI;30-34.9 kg/m^2), class II (BMI; 35-39.9 kg/m^2) or class III (BMI; ≥ 40 kg/m^2) obesity.
Results
Total of the 273 patients, 53 (19.4%) were male, 220 (80.6%) were female. 19 (7%) , 60 (22%), and 194 (71%) of the 273 patients had class I, II, and class III obesity, respectively. Ultrasonographically, the thyroid parenchyma was heterogeneous in 221 (92.9%) of the patients. But there was no statistically significant thyroid gland heterogeneity between the groups. Anti thyroglobulin antibody positivity was significantly higher in class III obese patients ($P=0.047$), but no significant difference was found in antiTPO antibody positivity and thyroid function tests between obesity classes. Also there was no significant difference between obesity classes and thyroid nodule features including; echogenicity, structure, halo sign, border regularity, presence of calcification and also thyroid nodule cytology. Conclusıon: Although we could not found a relationship between obesity classes and thyroid function tests and nodule features, most of the obese patients had parenchymal heterogeneity. Considering the increasing incidence of obesity and frequency of thyroid nodules, thyroid ultrasonography will be useful in obese patients.

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EP271

Prevalence of obesity complications in a group of obese patients undergoing bariatric surgery

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Introduction
Obesity is recognized as a continuously growing, global public health problem. It is associated with increased risk of a variety of acute and chronic disorders.
Objective
The aim of our work was to estimate the prevalence of obesity-related complications in a group of patients undergoing sleeve gastrectomy.
Methodology
Retrospective, descriptive study of a group of obese candidates for bariatric surgery recruited from the obesity research unit of the National Institute of Nutrition. All patients underwent a thorough interview, physical examination and biological analysis to rule out secondary obesity and to look for metabolic complications of obesity.
Results
Our study included 40 patients, 7 men and 33 women. The mean age of the patients was 34.6 years [18-57]. The mean BMI was 50.23 ± 8.27 kg/m^2. The mean waist circumference was 137.75 ± 16.09 cm. The prevalence of morbid obesity was 95%. Nearly two thirds of the subjects had a first degree family history of obesity. The prevalence of smoking and alcoholism was 27% and 2.5% respectively. The prevalence of metabolic complications of obesity was 7.5% for hyperuricemia, 37.5% for hypercholesterolemia, 67.5% for hypoHDLemia and 30% for hypertriglyceridemia. Concerning the disorders of carbohydrate tolerance, type 2 diabetes was found in 17.5% of patients, moderate fasting hyperglycaemia in 40% of patients and carbohydrate intolerance in 2 patients. Hypertension was diagnosed in 20% of patients. PCOS and fertility disorders were observed in 18% and 10% of obese women respectively. Digestive complications such as non-alcoholic fatty liver disease, vesicular lithiasis and gastroesophageal reflux were noted in 62.5%, 7.5% and 25% of cases respectively. Bone and joint complications were dominated by gonarthrosis in 57% of patients. obstructive sleep apnea syndrome (OSAS)was noted in 80% of patients with 32% mild, 22% moderate and 25% severe OSAS.
Conclusion
Our work demonstrates a significant prevalence of obesity complications in our population. This justifies the need for early and adequate management of obesity in order to prevent the occurrence of these complications.

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EP272

Impact of Ramadan fasting on the metabolic profile of obese patients

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Introduction
During Ramadan, patients often have an inappropriate eating behaviors which can have an impact on the metabolic profile, particularly in obese subjects.
Aim
The Aim of the study is to evaluate the effects of Ramadan fasting on the metabolic profile of obese patients.Patients and methods: This is was a prospective study including 109 obese patients with BMI ≥ 30 kg/m^2 aged 19 to 80 years of both sexes followed in the Endocrinology and metabolic diseases department of the IBN Rochd hospital center in Casablanca or seen at the consultation from March to May 2022. The patients were divided into 2 groups (fasting, non-fasting). A clinical and biological evaluation was carried out before and after Ramadan.
Results
The study population consisted of 109 patients, 80.7% were female and 19.2% were male. The average age was 55.92 ± 8.6 years. 87.15% of the patients were diabetic. Comparing the groups studied before and after Ramadan fasting, there was an increase in HbA1C in the non-fasting group (10.4 ± 2.13% against 9.4 ± 1.09%) ($P = 0.01$) compared to the fasting group where HbA1C remained stable (7.4 ± 0.89% vs 7.4 ± 1.82%). A slight decrease in fasting glycemia was objectified in fasting people ($P = 0.001$). Regarding anthropometric parameters, there was a slight weight loss (0.5-1 kg) with a decrease in BMI in the fasting group (33.1 kg/m^2 against 33.8 kg/m^2) ($P = 0.01$). In the fasting group, a slight increase in LDL levels was observed after Ramadan, but there was no significant change in total cholesterol, triglycerides and HDL levels.
Conclusion
This study indicated that Ramadan fasting caused a slight decrease in blood glucose and weight. Although there was a significant reduction in meal frequency, a slight increase in LDL was observed during Ramadan. It appears that the effect of Ramadan fasting on serum lipid levels may be closely related to diet.

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EP273

Ferrokinetic parameters in patients with diabetes mellitus type 2 and Covid-19

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Recent evidence points to a relationship between the severity of Covid-19 infection and iron metabolism. In patients with type 2 diabetes mellitus (DM 2), the prevalence of anemia of chronic diseases exceeds the general population indicators, which may be one of the factors determining the increase in mortality in this category of patients with Covid-19.
Aim
To determine the differences between markers of ferrostatus indicators in patients with DM 2 and Covid-19 depending on the value of blood oxygen saturation (SpO2).
Materials and Methods
The study included 84 patients with Covid-19 and DM 2. The levels of glycated hemoglobin (HbA1c), C-reactive protein (CRP), glomerular filtration rate (eGFR), interleukin6 (IL6), ferritin, serum iron (SI), transferrin, soluble transferrin receptors (STR), parameters of a general blood test were determined; SpO2 was assessed; damage to the lung tissue according to computed tomography scan of the lungs was evaluated. All patients we divided into 2 groups. Group 1 included patients with SpO2 $\geq$ 95%, group 2 - SpO2 $<$ 95%. The comparison groups did not differ in eGFR and HbA1c.
Results
Having analyzed the results of the study the following data were obtained. The data significantly differed between SpO2 values in groups 1 and 2 - 95.0 [95.0; 96.0]% vs 89 [87.0; 91.0]%,($P = 0.003$). Group 2 had the greatest damage to the lung tissue - 67.2 [65.0; 70.0]% vs 48.3 [40.0; 60.0]%, $P = 0.001$, maximum indices of inflammatory markers CRP (74.8 [69.0; 76.0] vs 45.4 [39.0; 53.0] mg/l, $P = 0.023$, IL6 (64.8 [59.0; 72 .0] vs 38. 2 [14.5; 51.0] pg/ml, $p = 0.031$ and minimal hemoglobin values (110 [101.0; 115.0] g/l vs 119 [108.0;121.0] g/l, $P = 0.017$). The ferrokinetic parameters differed significantly between the comparison groups. Ferritin above the acceptable target values was noted in two groups (in group 2-842.0 [663.0; 942.0] ng/ml vs 350.0 [310.0; 393.0] ng/ml, ($P = 0.003$)). The SI in group 2 was 0.6 [0.5; 0.9] vs 1.1 [0.8; 1.3], $P = 0.018$, the value of transferrin in group 2 was 1.3 [1.2; 2.0] vs 2.1 [1.9; 2.8], $P = 0.021$; STR in group 2 - 1.1 [0.8; 1.3] mg/l vs 1.3 [0.9; 1.4] mg/l in group 1, $P = 0.041$.
Conclusions
In the group of patients with type 2 diabetes and Covid-19 with SpO2 $<$89%, the most pronounced disturbances of ferrokinetic parameters were registered, which may be one of the factors determining the more severe course of Covid-19. STR is within the normal range, which indicates the absence of signs of iron deficiency anemia. Probably, there is a redistribution of iron in the body in patients with DM 2 and Covid-19 infection.

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EP274

New onset diabetes and COVID-19 and: what type?

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Introduction
During the COVID-19 pandemic, an increase of new-onset diabetes has been reported in various diabetes centers with many studies speculating an auto-immune-triggering mechanism while other studies hypothesizing an increase of type 2 diabetes (T2D).

Aim
The aim of this study is to compare the type of new-onset diabetes presenting with a diabetic ketoacidosis and its prevalence in the pre-pandemic vs pandemic COVID-19.
Methods
This is a comparative study of patients hospitalized in the diabetology department in the university hospital Farhat Hached of Sousse for a new-onset diabetic ketoacidosis in the pre-pandemic period (between March 2018 until March 2020) (G1) and 203 admitted during the pandemic period (between March 2020 until March 2022 (G2).
Results
A total of 340 patients were hospitalized in the diabetology department in the university hospital Farhat Hached of Sousse for a new-onset diabetic ketoacidosis, with 137 patients admitted in the pre-pandemic period (G1) and 203 admitted during pandemic period (G2). There was no significant difference in the prevalence of type 1 diabetes (T1D) between G1 and G2 as 54 out of 137 patients (39.41%) were T1D in G1 vs 81 out of 201 patients (40.2%) in G2. In the same way, the prevalence of T2D did not differ between the two groups with 83 out of 137 (60.5%) patients were T2D in G1 vs 120 out of 201 (59.1%) patients in G2 ($P=0.871$). Anti-GAD antibodies levels significantly increased during the pandemic period compared with the pre-pandemic period with a median value of 92.5 IQR [22.5-1074] in G1 vs 330 IQR [58.5-1795] in G2 ($P=0.021$). Anti-IA2 antibodies levels significantly increased as well during the pandemic period compared to the pre-pandemic period with a median value of 0 IQR [0-104.75] in G1 vs 93 IQR [0-3571] in G2 ($P=0.009$). No significant difference was found regarding anti-ZNT8 antibodies levels between the two groups ($P=0.475$).
Conclusion
Although the prevalence of T1D does not seem to increase during COVID-19, the increase of anti-GAD and anti-IA2 antibodies levels may reflect an increase in the intensity of auto-immune reaction of T1D during COVID-19.

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EP275

Stressful war conditions trigger eating disorders and worsen metabolic control in diabetic 2 patients

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Background and Aims
the war has become a stressful factor for many people in Ukraine. It is known that eating disorders (ED) might be triggered by a great stress. Binge eating disorder (BED) and night eating syndrome (NES) belong to hyperphagic ED mostly affecting those with obesity and diabetes type 2 (DT2). In our study we investigated how the war changed eating behavior and metabolic control in DT2 patients.
Materials and Methods
63 individuals (mean age – 54.1±7.3 years; BMI - 34.8±3.6 kg/m^2) with DT2 and without previous history of BED or NES were recruited into the study. All participants were receiving adequate therapy and did not stop taking antidiabetic medications during study period. They completed Binge eating scale-7 and Night eating questionnaire to diagnose BED and NES respectively. The level of glycated hemoglobin (HbA1c) before the war was checked in electronic healthcare system and measured again during war conditions.
Results
9 participants (14.3%) were screened positive with BED and 7 (11.1) – with NES. The current HbA1c level was significantly higher (7.8% vs 9.1%, $P<0.05$) when comparing with its level before the war. 12 (19%) participants reported about more frequent binge episodes that occur after the end of air raid warning. 5 (7.9%) individuals reported about binge episodes during the electricity blackout.
Conclusion
metabolic control of DT2 depends on a reaction to stressful life conditions. A serious stress factor for initiating BED and NES is war. Binge episodes occur more frequent during stressful events such as air raid warning or blackouts. War conditions require a tight metabolic control and an adequate stress management to avoid decompensation of diabetes and development of ED.

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EP276

The Mediterranean Diet: Effects on insulin resistance and secretion in subjects with obesity

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Introduction
A higher adherence (HA) to the Mediterranean Diet (MD) is associated to a lower risk of developing type 2 diabetes (T2DM). However it is less clear if this is caused by a "food cluster" (FC) or a single MD food effect on the insulin-resistance (IR) and/or on the insulin-secretion (IS).
Aim
This study investigated the association between MD adherence, IR and IS, indirectly measured, in subjects affected by obesity without diabetes (SNDO). The secondary aim was to determine if the FC or a single MD food is linked to IR and/or IS.
Methods
Participants underwent to an OGTT and an evaluation of IR (HOMA-IR and ISI) and IS (HOMA-β, OGIS e β-cell function). MD adherence was determinated through the PREDIMED questionnaire (0-5, 6-9, ≥10 for low (LA), intermediate (IA) and HA, respectively).
Results
Sixty-two SNDO were enrolled (9M/53F, 43.7±12 years, BMI 36±6.1 kg/m^2). The 18% of the SNDO had Impaired Fasting Glucose (IFG) whilst the 13% had Impaired Glucose Tolerance (IGT).Despite there were no significant differences in terms of BMI, SNDO with HA showed significantly lower values of HOMA-IR ($P<0.05$) compared to an IA and higher values of ISI ($P<0.05$) compared to a LA. MD adherence was inversely correlated to HOMA-IR (*r*:-0.400; *P*:0.004) and directly correlated with ISI (*r*:0.296, *P*:0.039). Among the MD food, fish was directly related with ISI (*r*:0.394, *P*:0.005) and inversely related with HOMA-IR (e *r*:-0.327, *P*:0.019) (Table 1).
Conclusions
A HA to the MD, and in particular the consumption of fish, is associated to a lower IR in SNDO and this was probably mediated by high content of polyunsaturated fatty acids.

Table 1 Participants' demographic and antropometric parameters and insulin-sensibility and secretion indexes

Parameters	Low adherence (PREDIMED: 0-5) ($n=12$)	Intermediate adherence (PREDIMED: 6-9) ($n=36$)	High adherence (PREDIMED: ≥10) ($n=14$)
Gender (M/F)	4/8	3/33	2/12
Age (Years)	41±14	45±12	45±11
BMI (kg/m^2)	39±7	36±6	35±6
WC (cm)	120±27	113±14	107±13
HOMA-IR	4.1±1.1	5.0±2.9	2.3±0.9‡
HOMA-β	18±5.5	20±5.9	10±4.1
OGIS (ml × min^{-1}× m^{-2})	395±62	406±72	440±52
ISI ((mg/dl)^2/(μU/ml)2) $^{-1/2}$)	2.7±0.9	3.0±2.0	4.5±2.6*
β-cell function (mg/μU)	0.5±0.2	0.6±0.5	0.8±0.3

The data are presented in terms of an average and SD.
*$P<0.05$ vs LA, one-way ANOVA with multiple comparisons adjustment (Least Significant Difference, LSD).‡ $P<0.05$ vs IA, one-way ANOVA with multiple comparisons adjustment (LSD).

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EP277

Relationship between diabetic microangiopathy and sexual dysfunction in women with type 2 diabetes

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Introduction
Female sexual dysfunction (FSD) is a frequent comorbidity in women with type 2 diabetes mellitus (T2DM), and is now increasingly considered a surrogate marker of endothelial dysfunction as well as a sentinel predictor of new-onset macroangiopathic events. Less attention, however, has been directed at the potential association of FSD and microangiopathy in hyperglycemic states.
Methods
We analyzed 30 consecutive female T2DM outpatients in whom FSD was assessed by the Female Sexual Function Index (FSFI) questionnaire. A score of

less than 26.55 characterizes FSD. Participants underwent a comprehensive interview, a complete eye examination and fasting blood tests. Socio-demographic and clinical characteristics were assessed during the consultation.
Results
Mean age and diabetes duration were 42.97 ± 6.6 years and 12.7 ± 6.21 years, respectively.Compared with patients without diabetic microangiopathy, those with any microangiopathy (odds ratio 12.6, $P = 0.007$) had an elevated risk of having sexual dysfunction. Women with diabetic nephropathy (odds ratio: 6, $P = 0.045$) and diabetic neuropathy (odds ratio 4, $P = 0.03$) had sixfold and fourfold increased odds of having sexual dysfunction, respectively, compared with those without diabetic nephropathy and neuropathy. Diabetic retinopathy, irrespective of presence or severity, was not independently associated with FSD ($P = 0.141$).
Conclusion
The presence and severity of diabetic nephropathy and neuropathy but not diabetic retinopathy is independently associated with self-reported female sexual dysfunction.

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EP278

Closed circuit hybrid control system IQ and Diabeloop in type 1 diabetics in open circuit prior treatment: data of 14 days

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Introduction
Achieving glycemic goals remains a challenge for many people with T1D despite recent technological advances. Integrated systems and closed loops pumps have shown significant improvements in glycemic control in clinical studies as well as in real life conditions.
Objective
Assess the performance of the systems Tandem Control-IQ and DIABELOOP in people with T1D comparing the glucosa readings before and after having the device for 14 days.
Research Design and Method
Retrospective observational study of 31 adults with long-evolving T1D, carriers of continuous insulin infusion pump (BICI) for at least 10 years and FSL2 to which a Dexcom G6 sensor is implanted and then the handle is closed. 19 patients (10 women) with a mean age of 49 years, and 29 years of evolution of diabetes were carriers of Tandem Control-IQ system and 12 patients (7 women) with a mean age of 46 years and 28 years of evolution of diabetes, carriers of DIABELOOP system (DBL). Both groups had at least 90% of the time in automatic mode. The data were analyzed by student T for paired samples.
Results
Both groups started from a time under the range (TBR) <54 in objective (IQ control 0.3%; DBL 0.9%) and only the IQ control group started from a TBR <70 in objective of 2%, being 4% in the DBL group. At 14 days, improvement was observed in the rest of the glycometric parameters, being significant in the control group IQ the increase of time in range (TIR, 59.9%-69.63%, $P = 0.0014$), the reduction of average glucose (GM 169.5-156, $P = 0.0075$) and the reduction of the glucose management index (IGG 7.8-%7.1%, $P = 0.0052$). Time above range (ART) 180-250 and > 250 was reduced without reaching statistical significance (ART 30.4%-24.4%, $P = 0.07$; ART >250 11.7%-7.7%, $P = 0.058$. The DBL group showed an increase in IRR (64.2%-70.4%), and a reduction in RRT <70 (4%-1.9%), RRT <54 (0.9%-0.3%), ART (30.1%-23.6%), ART >250 (9.2%-7.2%), LD (159-156 mg/), IGG (7.21%-7.08%) and coefficient of variation, being the only one that reached statistical significance (36.2%-30.6%, $P = 0.017$).
Conclusions
In our sample of patients with long-term T1D who had previously carried BICI and FSL2, loop closure was already associated at 2 weeks with an improvement in most of the glycometric parameters. 100% of patients in the Control IQ group achieve a TBR <54. Despite this, less than 45% of patients have all the parameters in objective, so we recommend an evaluation at 14-30 days after the system is installed for an early optimization of results.

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EP279

Footwear in a population of diabetic patients

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Introduction
Diabetic foot is one of the major complications of diabetes. Footwear has been found to be a precipitating cause of injury leading to lower extremity ulceration and amputation in people with diabetes. The aim of this study was to determine the suitability of footwear in a population of diabetic patients.
Methods
A cross sectional study including 150 patients with diabetes mellitus was conducted. Patients were asked about their follow-up during the previous year. An evaluation of risk of foot ulceration was performed based on the International Working Group on diabetic foot (IWGDF) classification. Podiatric and footwear examination were performed.
Results
The mean evolution of diabetes in these patients was 10.5 ± 7.8 years with a six-month follow-up rate in 66% of cases. Education on glycemic balance, lifestyle and dietary measures was done in 73.3% of cases. While education of podiatric risk of diabetes was only done in 16.7% of patients. Foot examination during the previous year was noted in only 12.7% of cases and 10% had a screening for diabetic neuropathy. Three-quarters of the population (74.7%) had no idea about the impact of diabetes on the foot. Regarding footwear, 89.3% of patients had no idea about the criteria for choosing a good shoe and 80.7% wore inappropriate commercial shoes. Appropriate therapeutic footwear was noted in 18% of patients and even among high-risk patients (grade 2 or grade 3 of IWGDF), only 6.9% wore orthopedic shoes for diabetic feet.
Conclusion
Majority (80.7%) of the participants wore inappropriate footwear and had no idea about the impact of diabetes on the foot. during follow-up, foot examination and patient education on podiatric risk were insufficient.

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EP280

After-stroke Rehabilitation outcomes of Diabetic patients

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Introduction
Stroke is the mean cause of acquired disability in adults. The objective of our study was to describe functional outcomes and complications in diabetic patients after stroke.
Patients and Methods
A descriptive study including diabetic patients followed in rehabilitation departement for vascular hemiplegia. Sociodemographic characteristics, patient history, and stroke history were collected. A functional assessment at 1 year after stroke was collected using the Barthel index, and neuro-orthopedic complications were noted in each patient.
Results
Sixty patients were included in this study. The mean age was 62 ± 12.6 years. At one year of evolution, orthopedic complications such as algodystrophy (22.5%), inferior subluxation of the humeral head (12%), spastic equinus of the feet (65%) were noted in our population. Mean Barthel index score was 45.5 meaning a moderate functional recovery.
Conclusion
Diabetes seems to worsen the long-term functional prognosis of stroke patients. This requires early and multidisciplinary management of patients with vascular hemiplegia to detect complications and improve functional recovery.

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EP281

Dupuytren's disease in a patient with type 2 diabetes mellitus: A case report

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Introduction
Dupuytren's disease (DD) corresponds to a chronic palpable thickening of the palmar aponeurosis which leads to different degrees of irreducible flexion of the fingers. It is one of the manifestations of hand syndrome in diabetes mellitus. We highlight through this report the occurrence of DD as a manifestation of diabetic hand syndrome in a patient with type 2 diabetes mellitus.
Observation
A sixty-six year old patient, truck driver, type 2 diabetic for twenty-two years, treated with oral antidiabetics, was admitted for treatment of an aseptic pseudoarthrosis secondary to surgical treatment of traumatic left tibial fracture. Medical history revealed poorly controlled diabetes, polyuro-polydypsia syndrome, and bilateral functional impotence limiting flexion of the first and second fingers. Clinical examination revealed bilateral flexion retraction of the first and second fingers, predominantly in the left hand, associated with palpable thickening of the palmar fascia. The rest of the osteoarticular examination did not reveal any other abnormalities except the fracture site in the left tibial bone. Biologically, the patient had an elevated HbA1c 9.7%, nonproliferative diabetic retinopathy, and chronic kidney disease at the stage of micro albuminuria. The diagnosis of fingers retraction in the context of DD with flexion deformities of the hands secondary to type 2 diabetes was retained. Therapeutic management was based initially on optimising glycaemic control and therapeutic education. Plastic surgery is planned on both hands.
Discussion
DD is a progressive fibrotic disorder of the fascia of the palm and fingers. Nodules and cords fixed to the skin and palmar fascia lead to flexural deformity of the fingers that disable normal movement of the hand, and result in the pathology of Dupuytren contracture. In people with diabetes, It mostly affects the third and fourth fingers, the thumb and the index are rarely involved. Several risk factors have been identified for DD; diabetes, increasing age, male, heavy alcohol consumption and smoking. The prevalence of DD in the diabetic population ranges from 20% to 63% depending on the series, compared to only 13% in the general population. The treatment of DD in diabetic patients does not differ from non-diabetic patients. Good glycaemic control is essential, Treatment can be medical and/or surgical. The decision to treat is guided by the functional discomfort degree.
Conclusion
DD is a fibroproliferative disorder often associated with diabetes and chronic hyperglycaemia. It causes a significant functional handicap requiring a multi-disciplinary management.

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EP282

« The renal function in patients with severe complications of diabetic foot syndrome with chronic kidney disease

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Aim
To study renal function in patients with severe complications of diabetic foot syndrome (ulcer, gangrene, amputation) associated with chronic kidney disease.
Material and Methods
91 patients with DM 2 were examined. The patients were divided into 4 groups:1 gr. – 25 patients with DFS complicated by ulcer, gangrene and amputation and in combination with CKD 4-5 stages on hemodialysis; 2 gr. – 25 patients with DFS complicated by ulcer, gangrene and amputation in combination with CKD stages 4-5 without hemodialysis; 3 gr - 20 patients with DFS complicated by gangrene and amputation without CKD.;4 gr - 21 patients with DFS, without severe complications, with the initial stage of CKD.Research methods- biochemical (bilirubin, direct, indirect, lipid spectrum, ALT, AST, PTI, coagulogram, blood sugar, glycated hemoglobin, urea, creatinine, GFR, wound pathogens, procalcitonin,interleukin-6,vascular endothelial growth factorVEGF-A and instrumental: ECG, MRI of the feet, Dopplerography of the main vessels of the legs, ultrasound of the internal organs, the fundus.
Results
The highest rates of fasting glycemia were observed in patients of group 2, that is, with DFS and CKD 4-5 stages without hemodialysis. Significantly lower hemoglobin values were also observed in this group of patients ($P<0.001$), glycated hemoglobin significantly higher values of urea, creatinine and GFR ($P<0.001$). All patients had significantly reduced values of HDL ($P<0.001$) and total cholesterol ($P<0.05$).
Conclusion
Biochemical parameters were significantly impaired in patients of group 1, that is, with DFS and CKD 4-5 stages on hemodialysis, which indicates the need for further research in this group of patients.

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EP283

Prevalence of malnutrition in elderly patients with diabetes mellitus in the hospital settings

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Objective
To estimate the prevalence of malnutrition in elderly patients with diabetes mellitus (DM) in hospital settings.
Patients and Methods
A retrospective descriptive study of 55 patients over 65 years of age who were hospitalized in the Endocrinology Department. The diagnosis of malnutrition was established according to the criteria proposed by the HAS 2021.
Results
The mean age of the elderly included was 71.4 ± 6.6 years with a female prevalence (53.7%). The age category >70 years represented 46.3% of our series. The mean HbA1C level was 11.2 ± 3.2%. Significant glycaemic imbalance (HbA1C >10%) was reported in 77.8% of cases. The majority of patients were on insulin therapy (84.9%). The average weight was 70.6 ± 15.5 kg corresponding to an average BMI of 26.7 ± 5.5 kg/m^2. Among the elderly with diabetes mellitus, 17.8% had a BMI <22. Significant weight loss was noted in 15.9%. The mean albumin level was 33.1 ± 5.8 g/l with hypoalbuminemia (<30 g/l) affecting 48.5% of patients. The overall prevalence of malnutrition was estimated at 37.5%. It was severe in 14.6%.
Discussion
The prevalence of malnutrition is estimated at 4-10% in the family home, 15-38% in institutions, and 30-70% in hospitals depending on the series. The consequences of poor nutrition are numerous and particularly detrimental in the elderly: increased mortality, frequency of complications during hospitalization (infections, bedsores, falls, etc.), and increased hospital expenditure. Nutritional screening is essential for all senior patients with DM, regardless of their caloric intake and BMI.
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EP284

HPLC-MS/MS in the diagnosis of factitious hypoglycemia: A case report

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Introduction
Artificial hypoglycemia (AH) is the intentional administration of insulin preparations or the use of oral hypoglycemic agents to lower blood glucose levels. It is one of the variants of Munchausen's syndrome. Hypoglycemia in non-diabetic patients is a blood glucose level of less than 3.0 mmol/l. AH among all causes of non-diabetic hypoglycemia (NDH) is approximately 4-11%. Identification of such cases is an urgent problem in the differential diagnosis of NDH, especially when insulin analogues are administered, since such insulin in the blood is not detected by many test systems.
Materials and Methods
A 28-year-old female patient complained of hypoglycemia up to 1.8 mmol/l, severe weakness, trembling in the body, which was stopped by taking fast carbohydrates. From the anamnesis it is known that the patient worked as a nurse, had long periods of disability, her family has patients with diabetes mellitus. The patient has been receiving treatment for conversion disorder for a long time. In 2015, diabetes mellitus (DM) has been diagnosed, but due to frequent hypoglycemic conditions, she received insulin episodically. MODY variants and autoimmune DM are excluded. In May 2022, during examination at the Endocrinological Research Center: HbA1c - 5.7%, C-peptide - 1.57 ng/ml, insulin

- 12.4 μU/ml, OGTT without deviations. A fasting test was initiated, after 42 hours hypoglycemia was recorded: glucose - 2.53 mmol/l, insulin 0.2 μU/ml, C-peptide 0.22 ng/ml. Hypocorticism and non-islet cell tumour hypoglycemia (NICTH) were excluded. Deliberate administration of insulin analogues is suspected. This blood sample was studied by HPLC-MS/MS, insulin Aspart was detected. When discussing the results, the patient denied the administration of insulin preparations. A conversation was held about the need to take drugs only as directed by a doctor and about the potential danger to life with self-treatment. It is recommended to continue the supervision of a psychiatrist.
Conclusion
The HPLC-MS/MS method greatly simplifies the diagnosis of factitious hypoglycemia and allows you to quickly identify not only oral hypoglycemic drugs, but also insulin analogues. In the case of diagnosing hypoinsulinemic hypoglycemia and excluding its more frequent causes (adrenal insufficiency and NICTH), it is advisable to study a hypoglycemic blood sample by HPLC-MS/MS to determine insulin analogues.

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EP285

Effects of Diabetes on Clinical Outcomes of Psoriatic Patients With Coronary Artery Disease

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Background
Psoriasis is associated with a heightened prevalence of cardiovascular risk factors, including diabetes. However, it is not clear whether diabetes will cause differences on clinical outcomes of psoriatic patients who have already suffered from coronary artery disease.
Methods
We conducted a retrospective cohort study of consecutive psoriatic patients with coronary artery disease between January 2017 and May 2022 in our hospital. The clinical records, laboratory measurements and coronary angiography reports were collected, and comparisons were made between patients with and without diabetes. The Cox regression analysis and Kaplan-Meier survival analysis were used to evaluate the association between diabetes and major adverse cardiovascular events (MACEs).
Results
Of the 307 participants, 147 patients had diabetes. Individuals with diabetes were more prone to be with hypertension ($P=0.045$), history of stroke ($P=0.041$) and peripheral vascular disease ($P=0.043$). The levels of low-density lipoprotein cholesterol ($P=0.039$), uric acid ($P=0.013$) and homocysteine ($P=0.006$) were higher in the non-diabetes group. Patients with diabetes were more likely to have lesions in the right coronary artery than those without diabetes($P=0.03$). After the mean follow-up of 35.32 ± 18.61 months, MACEs were more prone to occur in diabetes group than non-diabetes group (30.0% vs 19.2%, $P=0.032$). Kaplan-Meier estimates showed the same trend. The COX regression analysis showed that diabetes [hazard ratio (HR)$=1.661$, 95% confidence interval (95%CI): 1.025–2.692, $P=0.039$] was positively associated with an increased risk of MACEs. In the subgroup analysis, diabetes was associated with the occurrence of MACEs especially in men ($P=0.008$) and in patients without chronic kidney disease($P=0.021$).
Conclusion
In psoriatic patients with coronary artery disease, patients with diabetes were more likely to have lesions in the right coronary artery and diabetes can independently predict MACEs, especially in men and in patients without chronic kidney disease. To reduce the cardiovascular disease risk associated with diabetes, it is vital to increase awareness of the condition among these patients.

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EP286

Prediabetes remission after bariatric surgery: A 4-years follow-up study

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Background
Bariatric surgery leads to weight loss and to cardiometabolic risk improvement. Although prediabetes remission after bariatric surgery is biologically plausible, data on this topic is scarce.
Aim
We aimed to access pre-diabetes remission rate and clinical predictors of remission in a 4 year follow up period.
Methods
Observational longitudinal study including patients with morbid obesity and prediabetes submitted to bariatric surgery in our centre between January 2010 and December 2021. Prediabetes was defined as having baseline glycated haemoglobin (A1c) between 5.7% and 6.4% and absence of anti-diabetic drug treatment. We excluded patients submitted to gastric band surgery, or without A1c at baseline or first year of follow-up. We used logistic regression models to evaluate the association between the predictors and prediabetes remission rate.
Results
A total of 699 patients were included, 84% being female. The population had a mean age of 45.4 ± 10.1 years-old, body mass index of 43.8 ± 5.7 kg/m^2, and median A1c of 5.9 [5.8, 6.1]%. After bariatric surgery, prediabetes remission rate was 82%, 73%, 66%, and 58%, respectively at the 1st, 2nd, 3rd, and 4th years of follow-up. Gastric sleeve (GS) surgery associated to higher prediabetes remission rate than Roux-en-Y gastric bypass (GB) surgery since the 3rd year of follow-up. Men had a higher remission rate than female, except at 2nd year of follow-up. Younger patients presented a higher remission rate comparing to older patients since the 3rd year of follow-up.
Conclusion
Our results show a high prediabetes remission rate after bariatric surgery. The remission rate decreases along the follow-up period, although most of the patients uphold the normoglycemia. Prediabetes remission seems to be more significant in patients submitted to GS, male and younger patients. These results help to fill the gap in knowledge regarding the effect of bariatric surgery in prediabetes.

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EP287

Insulin therapy in elderly subjects with type 2 diabetes: Evaluation of injection techniques

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Introduction
Allowing to have a good glycemic control, presenting no contraindications and contributing to the optimization of the general and nutritional state, insulin remains a treatment of choice for the diabetic elderly. Proper injection technique is key to achieving and maintaining goal-level diabetes control. The objective of our study was to assess insulin injection techniques in elderly subjects with type 2 diabetes.
Methods
A cross-sectional study on type 2 diabetic insulin dependent elderly recruited from the outpatient endocrinology consultation over a period of 2 months from June 2021 to July 2021.
Results
We recruited 100 patients with a mean age of 70.8 ± 5.8 years and a sex ratio of 0.85. The mean durations of diabetes and insulin therapy were 15.67 ± 6.7 years and 7.69 ± 6 years, respectively. The mean level of HbA1C was 9.85 ± 1.7%. The majority of patients had uncontrolled diabetes (90%). Sixty-seven were on human insulin (67%) and thirty-three patients were on insulin analogues (33%). Pens were the instruments of injection for 33% of patients. The use of long needles of 6- and 8-mm was noted in 68% of patients although 4 mm needles are the recommended safer option. The patients were dependent on a third person to ensure the injection in 24% of cases. Abdomen and Arms were the preferred injection sites (76% and 59%, respectively). No patient used all four injection sites. Vial or cartridge of cloudy insulin was rolled or tipped less than 20 times in 2% and 3%, respectively. Extensive pen needle re-use (10+ times) for 29% of the patients exposed them to both higher intramuscular (IM) injection risk and lipohypertrophy (LH). Pain or Injection site bleeding was reported by 67% and 54% of patients, respectively. Nearly half of elderly diabetics (47%) skipped injections. In one-third of cases, patients had a history of severe hypoglycemia (35%).

Conclusion
According to our results, almost all aspects of insulin injection need to be improved in diabetic elderly subjects. This requires increased surveillance of the elderly, who face greater challenges in the feasibility of adequate injections.

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EP288

The impact of hybrid closed loop and predictive low-glucose suspend insulin pumps in the management of type 1 diabetes mellitus in children

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Introduction
Hybrid closed loop (HCL) systems are made up of continuous glucose monitoring (CGM) sensor, an algorithm that receives the readings from the CGM and an insulin pump able to deliver variable insulin doses according to the information received from the other two parts. Predictive low-glucose suspend (PLGS) insulin pump is able to stop the administration of insulin before hypoglycemia occurs. These new technologies are meant to improve the quality of life and help the patient achieve better metabolic control and avoid hypoglycemia.
Materials and Methods
We performed a longitudinal retrospective study and included children with type 1 diabetes mellitus (DM1) that were admitted to our department in order to initiate PLGS or HCL insulin pump therapy. We evaluated the patients at baseline, when the insulin pump was initiated, and at follow-up, after minimum 3 months from baseline. At both moments we assessed the hemoglobin A1c (HbA1c) level and downloaded the Carelink reports that reflected the previous 90 days. The reports were available at baseline and both at follow up in 18 patients and included the parameters time in range (70-180 mg/dl) (TIR), time below range (TBR), time above range (TAR) and coefficient of variations (CV).
Results
35 children were included in the study (65.7% females), and the mean age was 10.6 ± 3.7 years. HCL pump (Medtronic 780G) was initiated in 13 patients, and PLGS insulin pump (Medtronic 640G and 740G) in 22 patients. Mean follow-up time was 8.5 months. At follow-up, all parameters were improved. HbA1c decreased significantly (7 ± 0.9% vs 6.7 ± 0.5%, $P < 0.03$). Reports revealed that TIR increased significantly (69 ± 13.7% vs 76.6 ± 11, $P < 0.001$), with TBR and TAR significantly lower: TBR 5.3 ± 3.4% vs 3.28 ± 1.84%, $P = 0.02$ and TAR: 25.2 ± 15.5% vs 20.1 ± 10.9%, $P = 0.02$. CV also decreased significantly: 37.2 ± 3.6% vs 35.2 ± 4.2%, $P = 0.04$.
Conclusion
In conclusion, HCL and PLGS insulin pumps improve metabolic control in children with DM1 and they help them achieve targets regarding glucose variability and time spent in normoglycemia, therefor avoiding short-term and long-term complications.

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EP289

Evaluation of periodontal status in a population of obese patients: about 50 cases

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Introduction
The prevalence of obesity has increased dramatically in recent years. It is a risk factor for several chronic health problems. It is also associated with oral disease, particularly periodontal disease. Furthermore, periodontitis could contribute to obesity by inducing chewing disorders. The objective of this study was to determine the relationship between obesity and periodontal status in a group of obese Moroccan patients and to determine the main factors associated with this disease.
Materials and Methods
This is a case-control study conducted at the endocrinology and metabolic diseases department of the UHC Ibn Rochd in Casablanca and at the Ibn Rochd dental consultation and treatment center. It was spread over a year from September 2021 to September 2022.
Results
The prevalence of periodontitis was 98% in obese patients and 72% in the control group. The overall mean age was 37.54 years (± 12.6 years), that of obese patients was 39.18 years (± 12.16 years) and control patients was 35.9 years (± 13.1 years) with a clear female predominance whether in the group of obese patients or control cases. The average body mass index was 30.21 kg/m2 (± 8.4 kg/m^2), that of obese patients was 36.59 kg/m^2 (± 7.28 kg/m^2) with a statistically significant relationship between periodontitis and obesity ($P = 0.001$). Thus, there is a relationship between class 2 of obesity and the prevalence of the disease ($P = 0.014$). The majority of our patients were of low socioeconomic status (60% of cases) with evidence of a significant relationship ($P = 0.05$). Only a third of our population brushed their teeth correctly (31%). In the group of obese patients this percentage was 16%. The association between poor toothbrushing and periodontal disease was significant ($P = 0.04$). The bivariate analysis showed an increased risk of periodontal disease in the event of anterior tooth loss ($P = 0.01$). Receding gingiva was identified in 62% of obese patients and 54% of non-obese patients. The multivariate analysis did not show any statistically significant association between the different variables.
Conclusion
The susceptibility of obese patients compared to people of normal weight to chronic periodontitis prompts a systematic periodontal and dental examination of these patients in order to improve chewing ability. Hence the importance of multi-disciplinary management of these patients.

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EP290

Metabolic profile of morbid obesity compared to moderate and severe obesity

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Introduction
The prevalence of obesity is on the rise worldwide, including morbid obesity. It is responsible for many complications: metabolic, cardiovascular, respiratory, osteo-articular and psychiatric.
Aim
The aim of the study is to compare the metabolic profile of patients with morbid obesity (BMI ≥ 40 kg/m^2) with patients with moderate to severe obesity (BMI: 30 to 39.9 kg/m^2).
Patients and methods
This was a retrospective case-control study including 362 obese patients (BMI ≥ 30 kg/m^2).These patients were divided into 2 groups. Group (G1) included 262 patients with a BMI between 30 and 39.9 kg/m^2, and group (G2) included 100 patients with a BMI ≥ 40 kg/m^2.
Results
The average age of our patients was 55.12 years in G1 and 51.28 years in G2.A female predominance is noted in both groups. The average Body Mass Index in G1 was 32.5 kg/m^2 and 43.39 kg/m^2 in G2. Average waist circumference was higher in G2 (132.5 cm vs 108.46 cm). The prevalence of diabetes was 88.93% (G1) and 79% (G2) ($P = 0.2$). The prevalence of dyslipidemia was 74.04% (G1) and 73% (G2) ($P = 0.3$). Hepatic steatosis was present in 6.87% of cases in G1 and in 7% of cases in G2 ($P = 0.2$). Hyperuricemia was present in 13.7% of cases (G1) and in 15% of cases (G2). ($P = 0.2$).
Conclusion
Our study showed that morbid obesity is not significantly correlated with metabolic risk.

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EP291

Arterial stiffness in patients with type 2 diabetes mellitus at different stages of diabetic nephropathy

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Background and Aims
Arterial stiffness is associated with increased risk for target organ damage, cardiovascular events and overall mortality in the general population, patients with diabetes mellitus (DM) and patients with chronic kidney disease (CKD) of

all stages. The aim of this study is assessment of pulse wave velocity (PWV) in patients with type 2 diabetes at different stages of diabetic nephropathy and without it.
Materials and Methods
We examined 138 patients with DM type 2 aged 18 to 70 years. We divided the patients into two groups: the control group - patients without CKD and the main group - patients with CKD. The main group was also divided into 5 groups according to CKD stages by KDIGO (2012). In addition to routine tests for the diagnosis of CKD, we performed sphygmography (SphygmoCor XCEL, AtCor). Informed consent was obtaining from each patient prior to the study. To exclude the effect of smoking on arterial stiffness, former and current smokers were excluded from the study.
Results
Patient's average age was 51.6 ± 8.6 years in control group and 60.25 ± 8.05 years in main. The average duration of diabetes was 6.56 ± 4.8 years in control and 12.87 ± 7.34 years in main group. 55% of them were women ($n = 76$) and 45% were men ($n = 62$). Spearman's rank correlation analysis revealed a significant relationship between the PWV and age of the subjects ($r = 0.4$; $P < 0.001$); the duration of diabetes ($r = 0.3$; $P = 0.01$); estimated glomerular filtration rate ($r = 0.4$, $P = 0.004$) (Table 1). When examining subjects by age group, it was found that DM2 patients with CKD of the same age had a higher PWV compared to the control group (Table 2).
Discussion
Diabetic CKD patients present higher arterial stiffness than non-CKD counterparts do. With an increase in the stages of CKD and age, the PWV also increased. These finding suggest that the presence of CKD is another factor further contributing to the adverse profile of the macrocirculation in DM patients.
Keywords: diabetes mellitus, chronic kidney disease, pulse wave velocity, arterial stiffness

Table 1 PWV parameters in DM patients without CKD and in different stages of CKD

Group	$n=$	PWV (m/s)
Control	33	8.39 ± 1.50
CKD 1	24	9.06 ± 2.20
CKD 2	21	9.89 ± 2.67
CKD 3	25	10.14 ± 2.27
CKD 4	15	10.41 ± 2.31
CKD 5	20	10.75 ± 2.34

Table 2 Age dependence of PWV in DM2 patients with and without CKD.

Age	Control	Main	$P=$
60<	9.6 ± 1.2	10.5 ± 2.3	<0.05
45-59	7.9 ± 2.1	9.3 ± 2.4	<0.05
18-44	7.7 ± 1.8	8.2 ± 2.1	<0.05

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Prevalence of shoulder pain in people with uncontrolled diabetes in the western part of India: A cross-sectional study

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Introduction
Musculoskeletal disease is one of the common symptoms observed in people with diabetes. Shoulder pain is found to be the most common symptom and can lead to hindrance in daily activities that can directly or indirectly influence the metabolic processes of our body affecting the quality of life. Hence, we studied the prevalence of shoulder pain and its functional limitations among patients with uncontrolled diabetes mellitus (DM).
Materials
This cross-sectional study was conducted in OAK Hospital and ICON Multispecialty Hospital, Dombivali from October 2022 to December 2022. Included all patients with uncontrolled DM (HbA1c > 8.5) who have visited the clinic. Responses were captured via Interviews using a previously validated questionnaire, the American Shoulder and Elbow Surgeons Evaluation Form. Informed consent was obtained from the participants.
Results
A total of 125 patients were included in the study; 72 (57.6%) were females and 130 (42.4%) were males. Around 76 (60.8%) of the patients were aged 41-60 years. The people with T2DM (90.4%) were the majority. The mean HbA1c level was 10.12%. Shoulder pain was present in 45 (36%) patients. Amongst them, 35.5% were between 41 and 60 years and 48.8% were between 61 and 80 years. The mean shoulder pain intensity for all patients was 5.61 ± 3.1. There was a significant correlation ($P < 0.05$) in different age groups.
Conclusions
Shoulder dysfunction with its increased prevalence needs an early diagnosis and management. It is advised to include screening, prevention, and rehabilitation strategies for shoulder dysfunction in diabetic care programs to improve the daily lifestyle of the patients.
Keywords: T2DM, Shoulder Pain, Quality of life.
Reference
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Precipitating factors and symptoms in patients with diabetic ketoacidosis

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Aim
The aim of the study was to determine the most common precipitating factors and symptoms of diabetic ketoacidosis and whether there is a difference in regard to age, gender and severity of diabetic ketoacidosis.
Patients and Methods
Medical records from 1 January 2017 to 31 December 2019 were reviewed and patients with the diagnosis of diabetic ketoacidosis were selected.
Results
The study included 52 patients. The median age was 34 years (interquartile range 21-56 years). There was no statistically significant difference between male and female gender. The severity of diabetic ketoacidosis was moderate in the majority of cases (65.4%; $P = 0.005$). The most common precipitating factor was infection (61.7%). In patients with moderate diabetic ketoacidosis, respiratory infections were more common, while gastrointestinal infections were more common in severe diabetic ketoacidosis (33% and 25%; $P = 0.03$). Nausea (median age 32 years; $P = 0.004$) and vomiting (median age 31 years; $P = 0.01$) were more common in the younger age groups, while altered mental status was more common in the older age group (median age 61 years; $P = 0.001$).
Conclusion
Infection was the most common precipitating factor. The most common symptoms in the younger age groups were nausea and vomiting and in the older age group altered mental status.
Keywords: diabetes mellitus, diabetic ketoacidosis, infection, nausea, vomiting
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Glucose and sodium levels as disease outcome predictors in critically ill patients

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Aim
The main aim of this study was to examine the association of glucose and sodium level with diagnosis and disease outcome of critically ill patients.
Patients and Methods
The glucose and sodium concentration of 283 patients admitted in critical condition to the Intensive Care Unit of the Department of Internal Medicine in a period from 1 November 2015 to 28 February 2017 were reviewed.
Results
Most common diagnoses in critically ill patients were acute kidney injury (26.1%) and sepsis (including septic shock) (22.3%). Significantly lower glucose concentration was observed in patients with acute kidney injury ($P = 0.02$), whereas patients in sepsis and septic shock had significantly higher sodium concentration ($P = 0.04$). Higher glucose level was related to higher mortality rate ($P = 0.001$). On the other hand, sodium level was not significantly associated with survival. Higher mortality as well as higher glucose concentration were more common in patients older than 65 years ($P < 0.001$).

Conclusion
This study has shown significantly lower concentrations of glucose in patients with acute kidny injury, whereas in patients older than 65, glucose concentration was significantly higher. Patients in sepsis and in septic shock have shown significantly higher concentrations of sodium. Higher concentration of glucose was connected with higher mortality in elders, where as concentration of sodium did not show connection with morality.
Keywords: critical illness; glucose; intensive care unit; sodium
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Place of podoscopic examination in diabetic foot
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Introduction
Diabetic foot is a public health problem. It can cause serious complications leading to amputation. Diabetic neuropathy (DN) is the main factor of ulcerations. Plantar hyperpressure is an aggravating factor.
Aim
The aim of our study was to screen for various deformities of the diabetic foot through podoscopic evaluation.
Patients and Methods
We conducted a bicentric cross sectional study over a three month period including diabetic patients. Detail history including socio demographic data, characteristics of diabetes and the follow-up story were collected. Podiatric examination was performed using a tangential lighting podoscope.
Results
We included 150 patients. Their mean age was 56.91 ± 12.6 years with a range of 20 to 86 years. Half of patients were using oral medications, 28% were using insulin therapy and 21.3% were using both oral and insulin therapies. Diabetic neuropathy was found in 32.7% of the population. The podiatric examination revealed plantar hyperkeratosis in 84% of patients, dry skin in 46% and mycotic lesions in 27.3%. Plantar perforation was noted in 2 patients, and toe amputation in 4 patients. The main hyper pressure zone found was regarding the second metatarsal head (52%). Foot orthotics were prescribed in 18% of patients.
Conclusion
Podiatric examination is essential to detect areas with hyper pressure at risk of hyperkerathosis and plantar perforation. It allows preventive measures, including devices to reduce hyperpressure and prevent complications.
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Diabetic Ketoacidosis on Orbital Cellulitis with Mucormycosis: A Case Report
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Introduction
Mucormycosis is a rare, devastating, fungal infection, which disproportionately affects non-controlled diabetic patients, notably during ketoacidosis. It is a potentially lethal disease. The diagnosis and treatment of mucormycosis remain a challenge because of the nonspecific clinical presentation. We discuss the clinical features and management modalities of this case.
Case
We report the observation of a 41 years old male patient, who had had type 1 diabetes mellitus for 21 years under insulin .He consulted the emergency room for diabetic keto-acidosis (DKA) on left unilateral orbital cellulitis of sudden onset. Clinically the patient was febrile with palpebral oedema, chemosis and painful ophthalmoplegia. The initial orbital CT scan was in favor of chandler stage 1 pre-septal cellulitis of the left eye with grade 1 exophthalmos probably of sinus origin. The patient was immediately put on parenteral tri-antibiotherapy with a worsening of the inflammatory signs clinically, biologically and by the extension on the CT scan of the cellulitis in the retro-septal area with ethmoidal and orbital abscesses complicated by septic thrombosis of the cavernous sinus and the internal carotid artery, intracerebral collections an. After mycological sampling of the inner part of the upper eyelid concluded to be *Rhizopus microsporus*.The patient benefited from endo-nasal surgical debridement and effective antic-oagulation associated with liposomal amphotericin B for 10 days and then classical amphotericin B for 2 months. The subsequent evolution was favourable after broad surgical drainage, with disappearance of inflammatory signs, but blindness is definitive.
Discussion and Conclusion
Mucormycosis is a rare fungal infection that should be considered. The diagnosis, often difficult, must be made as early as possible. Poorly controlled diabetes mellitus is one of the main risk factors. The treatment, initiated as a matter of urgency, combines antifungal treatment, surgical debridement and correction of predisposing factors. The vital and functional prognosis remains severe in most cases.
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Prevalence of symptoms and precipitating factors of Diabetic Ketoacidosis in diabetic patients
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Background/Aim
Since diabetes is the most common endocrine disorder and the diabetic ketoacidosis (DKA) is considered as a medical emergency, our aim was to determinate the frequency of symptoms and precipitating factors of DKA in type 1 and type 2 diabetes
Methods
This is a retrospective cross-sectional descriptive study concerning all patients hospitalized in the Endocrinology Department for DKA between August 2021 to December 2022.We compared the differences in prevalence, of precipitating factors and clinical presentations between type 1 (T1D) and type 2 (T2D) diabetes.
Results
Out of 30 patients, 19 (63.3%) patients had type 1 diabetes and 11 (36.7%) had type 2 diabetes. The mean age of patients was 26.7 ± 10.4 years (type 1 diabetes 22 ± 6.5 years; type 2 diabetes 34.9 ± 11 years). The most common symptoms of patients were polyuria and polydipsia seen in 56.7% of patients (T1D: 42.1% vs T2D:81.8%) at the first time of their admission. Nausea and vomiting, abdominal pain, fever and dehydration were observed in 43.3% (T1D:47.4% vs T2D:36.4%), in 26.7% (T1D:31.6% vs T2D:18.2%), in 10% (T1D:10.5% vs T2D:9.1%) and in 6.7% (T1D:5.3% vs T2D:9.1%) of patients, respectively. Polyuria and polydipsia were the only symptoms statistically different between the two groups ($P = 0.03$). The most common precipitating factor of DKA was therapy discontinuation seen in 43.3% of patients (T1D:52.6% vs T2D:27.3%). First presentation and infections were observed in 33.4% (T1D:26.3% vs T2D:45.5%) and in 23.3% (T1D:21.1% vs T2D:27.3%) of patients, respectively. The differences in precipitating factors of DKA between the two groups were no significant.
Conclusion
The most common precipitating factor of DKA was therapy discontinuation mainly among T1D. More information about diabetes mellitus among population is necessary to reduce the incidence of DKA.
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MRI for diagnosis of early-stage Charcot foot
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Purpose
The purpose of the study is to evaluate the results of MRI of studies in patients with the active stage of the Charcot foot.
Material
The material of the study 29 patients (prospectively) were examined with type 2 diabetes with the active stage of the Charcot foot in the period 2021 at the

RSSNPMC of endocrinology, in the department of diabetic foot. The control group amounted to 20 healthy persons.
Background/Aim
Biochemical (bilirubin, straight, indirect, lipid spectrum, ALT, AST, Coagulogram, blood sugar, glycated hemoglobin, urea, creatinine). Instrumental: ECG, MRI, Dopplerography of the main vessels of the legs, ultrasound of internal organs, DEXA, ocular fundus.
Research Results
In the patient's group, 21 men were observed (the average age of 69.6 years) and 8 women (the average age 68, 9 years). The duration of the DM2 was 21/19, respectively.. The duration of the SDS was 9/7 years, respectively. On MRI we found location of bone marrow abnormality (edema shown in fluid sensitive sequences, and reduction of fatty bone marrow shown in T1 sequences). Pattern tends to be periarticular. In all patients were involved several joints and bones (mostly tarso-metatarsal joints and metatarsophalangeal joints).
Conclusions
During early-stage Charcot foot, CT does not play an important role for imaging since bone marrow and soft tissue changes can be better visualized using MRI. CT may be used in later-stage Charcot foot for better visualization of bony proliferations and consolidation. Recognizing this disease in early stages prevents a delayed onset of an appropriate therapy and helps minimizing the disability of these patients.

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Mucormycosis Rhinosinusitis in Diabetic patients

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Purpose
Mucormycosis is a rare and potentially fatal invasive fungal infection which usually occurs in diabetic and other immunocompromised patients. This infection is associated with high morbidity and mortality rates. Prompt diagnosis and rapid aggressive surgical debridement and antimycotic therapy are essential for the patient's survival .The purpose of this study was to expose the clinical feature, and to discuss the specificities management of mucormycosis in the setting of diabetes.
Material and Methods
This study was based on retrospective review of six diabetic patients who suffered from mucormycosis rhinisinusitis, over 22 years period (2000-2022).
Result
The mean age was 41 years with male predominance (4 males per 2 females), the average duration of diabetes follow up was over 10 years. We noticed an orbital involvement in one case. Rhinocerebral mucormycosis was diagnosed in one patient. The infection was limited to the rhinosinus space in 4 cases. The causative agent was, exclusively, Rhizopus arrhizus. Paranasal CT scan was performed for all our patients. In all cases, surgical evaluation was immediately performed for debridement of the necrotic tissues, and multiple biopsies were performed for diagnostic purposes. The medical treatment was based in intravenous liposomal amphotericin B. Nephrotoxicity were noted in 2 cases, with hepatic insufficiency in one of them. The main complication was septicaemia, seen in one case, after one week evolution. We noted a complete recovery in 5 cases. Despite an early diagnosis and rapid treatment the course of the disease has been marked by the death of one patient who had a cerebral involvement.
Conclusion
Mucormycosis rhinosinusitis is a disease with a rapid evolution and high morbidity and mortality rates, especially if there is an orbito – cerebral involvement. Therefore, it would be necessary in all diabetic patients, with sinus symptoms, headaches, visual changes, to suspect a mucormycosis, and perform immediately the appropriate surgical and medical management.

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Predictive factors of diabetic foot ulcer recurrence

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Introduction
Diabetic foot is a major health problem, especially when it is complicated by recurrences. It entails a heavy economic burden for the patient and for the health system. The objective of this work is to study the characteristics of diabetic patients with recurrent foot ulcer as well as the predictive factors of recurrence.
Material and Methods
This study is a retrospective cohort study from January 2020 to May 2022 involving patients hospitalized in our department for diabetic foot ulcer. The analysis was performed using SPSS 21 software.
Results
Out of a total of 175 patients, 64 patients presented a recurrence, i.e. 36.5%. The average age was 59 years with a sex ratio M/F of 1.5. The average duration of diabetes was 18 years. Regarding the characteristics of the patients, 87.5% were type 2 diabetics with an average HbA1c level of 8.9%. Regarding degenerative complications, 85.9% had a diabetic retinopathy and 66.15% presented peripheral neuropathy, while 68.7% had peripheral artery disease. Concerning the ulcers, 48.4% had neuropathic plantar ulcers while 39% had ischemic ulcers. Among the patients, 54.6% presented foot deformities, 18.7% presented a Charcot foot and 20.3% had a history of amputation. The evolution was favorable in 93.7%. Predictive factors of recurrence were age ($P=0.01$), diabetes duration ($P=0.00$), glycemic imbalance ($P=0.00$), microangiopathy mainly diabetic retinopathy ($P=0.00$) and peripheral neuropathy, existence of peripheral artery disease ($P=0.00$) and low socioeconomic status ($P=0.00$). Charcot's foot, foot deformities and previous amputation were also predictive factors.
Conclusion
Recurrences of diabetic foot ulcers are quite common. Reducing them requires action on modifiable predictive factors and this through effective prevention and education.

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Potential risk factors of hypokalemia in patients with diabetic ketoacidosis

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Background/Aim
Diabetic ketoacidosis (DKA) is a life-threatening acute complication of diabetes. Our aim was to study the clinical features of DKA and precipitating factors responsible for DKA in diabetic patients.
Methods
This is a retrospective cross-sectional descriptive study concerning all patients hospitalized in the Endocrinology Department for DKA between August 2021 and December 2021. Initial kalemia levels (k +) on presentation were determinated on AU 680® Beckman Coulter. Hypokalemia was defined using the criteria set forth by the American Diabetes Association (ADA) as measured serum potassium less than 3.3 mmol/l. The common clinical presentations, precipitating factors and the mean of Glycemia between diabetes who presented hypokaliemia (G1) and those with normal k + (G2). The data were analyzed using SPSS25.
Results
Out of 30 patients, 19 (63.3%) patients had type 1 diabetes and 11 (36.7%) had type 2 diabetes. Mean age was 26.7 $\pm$10.4 years. There were12 (40%) males and 18 (60%) females. The mean of BMI was 20.5$\pm$3.4 kg/m^2. The mean potassium level was 3.73 mmol/l (range 2.3 to 5.3; SD +/- 0.72). Among patients, 26.7% (T1D:50% vs T2D:50%), had hypokalaemia (k + < 3.3 mmol/l). The mean age was 26.7 $\pm$10.4 years (type 1 diabetes 22$\pm$6.5 years; type 2 diabetes 34.9$\pm$11 years). The most common symptoms of patients were polyuria and polydipsia seen in 56.7% (G1:37.7% vs G2:63.6%) at the first time of their admission. Nausea and vomiting, abdominal pain, fever and dehydration were observed in 43.3% (G1:75%vs G2:25%), in 26.7% (G1:62.5% vs G2:0%), in 10% (G1:12.5% vs G2:9.1%) and in 6.7% (G1:0% vs G2:9.1%) of patients, respectively. Abdominal pain, nausea and vomiting were the symptoms statistically different between the two groups ($P<0.0001$, $P=0.035$ respectively). The most common precipitating factor of DKA was therapy discontinuation seen in 43.3% of patients (G1:37.5%vs G2:45.5%), first presentation and infections were observed in 33.4% (G1:25%vs G2:36.4%). and in 23.3% (G1:37.5%vs G2:18.2%), of patients, respectively. The differences in precipitating factors of DKA between the two groups were no significant.
Conclusion
Hypokalemia was observed in 26.7% of patients with DKA. Abdominal pain, nausea and vomiting are more frequents in patients who presented hypokaliémia. Further research is needed to better determine the risks and benefits of administering insulin before obtaining serum potassium values.

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EP302

Assessment of the nutritional status of elderly diabetics

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Objectives
The aim of our study was to assess the nutritional status of elderly diabetics.
Methods
This was a descriptive cross-sectional study conducted at the National Institute of Nutrition in Tunis including 40 diabetics aged over 65 years. All patients underwent anthropometric measurements (weight, height, body mass index (BMI)), a biological assessment (fasting blood glucose, glycated haemoglobin (HbA1c)), a dietary survey and an assessment of nutritional status using the Mini Nutritional Assessment MNA questionnaire.
Results
The mean age of the patients was 71.3 ± 5.5 years, the mean HbA1c was $10.32 \pm 2.12\%$. The dietary survey revealed hypocaloric and hypoprotein intake in 25% and 32.5% of patients respectively. The mean BMI was 31.25 ± 5.97 kg/m^2, we found weight loss $>5\%$ in one month and $>10\%$ in 6 months in 10% and 7.5% of patients respectively. Referring to the MNA; almost two thirds of the patients were at risk of malnutrition and 7.5% had a poor nutritional status. Patients with a normal nutritional status according to the MNA had a better glycaemic control than patients with a risk of malnutrition or undernutrition ($HbA1c = 8.97 \pm 1.19\%$ vs $10.9 \pm 2.17\%$, $P = 0.04$). Furthermore, the risk of malnutrition increased significantly with BMI ($P = 0.011$). In contrast, we found no relationship between caloric intake, protein intake and nutritional status according to MNA.
Conclusion
Undernutrition is common in poorly balanced elderly diabetics, justifying a systematic assessment of nutritional status and optimal glycaemic control in these patients.

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Indicators of osteocalcin and adiponectin in pregnant women with type 1 diabetes mellitus

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Introduction
The relationship between indicators of carbohydrate, fat and bone metabolism is beyond doubt. It is known that osteocalcin, overcoming the blood-brain barrier, can affect the development of the fetal brain. Adiponectin is currently being considered as a biomarker for pregnancy complications. These facts determined the purpose of the study.
Aim
To study the content of osteocalcin and adiponectin in pregnant women with type 1 diabetes (T1DM).
Materials and Methods
A prospective single-center study was conducted on the basis of the Republican Scientific and Practical Center "Mother and Child" among pregnant women with a full-term pregnancy. We compared 2 groups of pregnant women: group 1 (Gr 1) - pregnant women with T1DM ($n = 37$) and group 2 (Gr 2) - pregnant women without diabetes ($n = 31$) whose levels of osteocalcin and adiponectin in venous blood were determined the day before delivery. Women of both groups were comparable in terms of pregravid body mass index (BMI) ($P = 0.263$), which was in the normal range (BMI <25) and delivery time. Glycated hemoglobin in pregnant Gr 1 was 6.6% (6.0–7.4%).
Results
The level of osteocalcin in Gr1 was 1.04 (0.58–2.49) ng/ml, and in Gr 2 it was 2.05 (0.87–7.64) ng/ml and was statistically significantly less against the background diabetes ($P = 0.013$). The level of adiponectin in Gr1 was 20.59 (12.4–27.07) mcg/ml, and in Gr2 it was 9.7 (9.04–13.35) mcg/ml and was statistically significantly higher ($P < 0.001$) in pregnant women with type 1 diabetes.
Conclusions
In our study, pregnant women with type 1 diabetes had lower levels of osteocalcin than healthy pregnant women, which can be attributed to the effect of hyperglycemia. Higher levels of adiponectin in pregnant women with type 1 diabetes seem to be associated with autoimmune processes, which requires further study.

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Neonatal diabetes mellitus in a patient with a novel heterozygous mutation in GATA6

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Transient neonatal diabetes mellitus (TNDM) occurs in 50-60% of all cases of neonatal diabetes mellitus (NDM). The most common cause of TNDM (70%) is almost invariably associated with defect in chromosome 6 and mutations in the *KCNJ11, ABCC8, INS, NHF1B* etc. genes. TNDM is caused by mutations in the GATA6 gene in rare cases. This gene encodes a transcription factor that is important for the development of the hematopoietic, cardiac and gastrointestinal systems.
Clinical Case
Proband is a female born at 35 week of gestation with intrauterine growth retardation (weight 1580 g (SDS -2.29), length 40 cm (SDS -2.65)) via cesarean section. The proband was fedded using tube feeding in neonatal period. The proband was diagnosed with hyperglycemia 29.6 mmol/l in the neonatal period, insulin therapy was started. Insulin was stopped in 1 month of life. Normoglycemia was observed. Family history of diabetes was negative. The proband was relapse of diabetes in 3 years old after a respiratory infection. She had polyuria, polydipsia and weight loss. HbA1c 11.5%, glycemia 18.6 mmol/l. Insulin (As part, 0.4 U/kg/day) was started. Fasting C-peptide 0.69 ng/ml, stimulated C-peptide in 120 min - 2.32 ng/ml. Specific islet antibodies (GADA, IA2A, IAA, ZnT8A) were negative. Pancreatic hypoplasia was diagnosed due to ultrasound. Genetic test (NGS 27 genes) was performed, no mutations were detected. Proband had extrapancreatic features: moderate growth retardation (growth SDS -1.95), patent ductus arteriosus, mitral valve prolapse, gallbladder agenesis, umbilical hernia, autoimmune thyroiditis. At the age of 8 years (diabetes duration was 5 years) patient was treated fast acting insulin Aspart, 0.7 U/kg/day. HbA1c 5.2%, fasting C-peptide 0.71 ng/ml, stimulated C-peptide in 120 min – 0.9 ng/ml. Whole-exome sequencing revealed novel pathogenic heterozygous mutation c.1302+4 1302+7del in exon 3 of the GATA6 gene, leading to a deletion of 4 nucleotides.
Conclusion
TNDM is rarely caused by mutations in the *GATA6* gene. The development of NDM due to mutations in the *GATA6* gene is probably associated with pancreatic hypoplasia. Diabetes associated with mutations in the *GATA6* gene is progressive. Patients with mutations in the *GATA6* gene have extrapancreatic features (congenital heart defects, gallbladder agenesis, umbilical hernia).

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EP305

Study of clinical and laboratory parameters in patients with COVID-19, taking into account the outcome of the disease

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According to modern concepts, stress hyperglycemia and diabetes mellitus (DM) are often found in hospitals and are associated with an increase in complications, length of hospitalization and mortality. The analysis of data on the COVID-19 pandemic indicates a worse prognosis and a high risk of hospital complications in patients with DM.
Aim
The aim of the study was to evaluate clinical and laboratory parameters that can be used to predict an unfavorable outcome of Covid-19.
Materials and Methods
A retrospective analysis of data from of 320 patients with Covid-19 infection, who was treated in the intensive care unit of the infectious Minsk hospital from June 2020 to March 2022, was carried out. The following groups were formed: 224 people with transient hyperglycemia (the main group); 51 patients with DM (comparison group); 45 people without glycemic disorders (control group). Also, patients were divided into subgroups based on the outcome (favorable or unfavorable outcome).
Results and Discussion
The mean age of deceased patients was significantly higher than that of surviving patients (67.0 (59.3; 74.0) years vs 57.0 (47.0; 66.8) years, $P < 0.001$), indicating the fact that the age of the patient is a prognostically unfavorable criterion for the outcome of the disease. Among deceased patients, higher glycemic values were

recorded, mainly in the DM group (20.9 (14.9; 23.9) mmol/l vs 13.4 (10.9; 17.7) mmol/l, $P=0.005$). Patients with an unfavorable outcome had differences in laboratory parameters already on the first day of hospitalization and was characterized by higher values of inflammation indicators (leukocyte level ($P=0.002$), LDH ($P=0.008$), CRP ($P=0.003$), procalcitonin ($P<0.001$), D-dimers ($P<0.001$), as well as greater severity of lymphopenia ($P=0.006$). In patients with an unfavorable outcome, starting from the 4th day of stay in the ICU, a tendency to persistent hyperglycemia was noted. Negative dynamics of glycemia was noted on day 7 in the observation groups, depending on the unfavorable outcome: DM (13.4 (8.1; 19.8) vs10.1 (5.6; 11.9), $P=0.014$), HG (8.7 (7.2; 11.8 6.4 vs (5.7; 7.6), $P=0.017$), control (6.2 (4.0; 7.2) vs 5.3 (5.1; 5.9), $P=0.123$). Moreover, the glucose levels in the DM and HH group increased most significantly on day 7.

Conclusions

Thus, diabetes mellitus and in-hospital hyperglycemia are significant risk factors for the severe course of COVID-19, as well as its poor outcome. From the 4th day patients with an unfavorable outcome showed a tendency to persistent hyperglycemia, which potentially indicates its role as a prognostic parameter.

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EP306

Maturity Onset Diabetes of the Young (MODY) associated with mutations in the Regulatory factor X6 (RFX6) gene: A case report

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Introduction

Maturity onset diabetes mellitus of the young (MODY) is a form of monogenic diabetes characterized by pancreatic B-cell dysfunction. The most common subtypes are caused by mutations in the genes encoding glucokinase (GCK) and hepatocyte nuclear factor (HNF1a, HNF4a), although unidentified genes are also involved. Regulatory factor X6 (RFX6) is a transcription factor gene which has an important biological role in B-cell formation and function. Biallelic mutations in RFX6 cause Mitchell–Riley syndrome, characterized by neonatal diabetes, pancreatic hypoplasia, gallbladder agenesis or hypoplasia, and intestinal atresia. Heterozygous RFX6 mutations have been identified in MODY cases.

Case Report

A 19-year-old female, with no past medical history, was referred to the emergency department for diagnostic evaluation of hyperglycemia, which was found in a medical checkup. She had been experiencing symptoms of diabetes mellitus (polyuria, polydipsia and weight loss of 5 kg) over the previous 2 months. Family members, including her sister, mother, and maternal grandfather had a history of diabetes. Her height was 156 cm, and her weight 59 kg, with a body mass index of 26 kg/m^2. Admission laboratory test reports included elevated plasma glucose and HbA1c levels (324 mg/dl and 11.4% respectively); and a diabetes mellitus diagnosis was made. No diabetic ketoacidosis was present. The patient was started on insulin therapy with a total dose of 17 units per day. She was evaluated in the Department of Endocrinology 1 year after the onset of diabetes. She had discontinued insulin therapy and was not receiving further treatment. HbA1c had decreased to 6.5% and her C-peptide level was 1.32 ng/ml. There were no islet cell antibodies (ICA), glutamic acid decarboxylase (GAD) antibodies, or insulinoma-associated (IA-2) autoantibodies found. Genomic sequencing was performed in a panel which included 50 genes associated with monogenic diabetes mellitus. The analysis identified a heterozygous RFX6 mutation (c.541C>T, p.Arg181Trp) in the proband, which carried no pathogenic variants in other tested genes.

Conclusion

We describe a case of MODY due to a heterozygous RFX6 mutation p.Arg181Trp. RFX6 mutations have been associated with non-syndromic MODY with low penetrance and post-pubertal onset. Our report supports the evidence of causal relationship, although further studies are needed to define the association and to determine the appropriate therapeutic approach for these patients.

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EP307

Factors influencing Tunisian diabetics' knowledge and attitudes: Cross-sectional study

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Objective

To determine the factors influencing the level of knowledge and attitudes of diabetics consulting in first and third line in the Sousse region (Tunisia).

Patients and Methods

We undertook a cross-sectional study. Diabetics were included by proportional sampling in 11 basic health centers and six hospital departments and outpatient clinics of the university hospital centers of Sousse. The developed questionnaire was self-administered in Arabic. It included patient demographic characteristics data, diabetes-specific data, the Simplified Diabetes Knowledge Scale to measure knowledge and the Diabetes Attitude Scale-3 to measure attitudes towards diabetes.

Results

We collected 1007 diabetics. Factors influencing the acquisition of a good level of knowledge were high school (adjusted OR = 2.23) or university education (adjusted OR = 3.55), living in an urban area (adjusted OR = 2.49), and stable employment (adjusted OR = 3.04). Type 2 diabetes (adjusted OR = 4.02), insulin therapy (adjusted OR = 4.14), previous therapeutic education sessions (adjusted OR = 1.55), self-monitoring of blood glucose (adjusted OR = 2.67), and regular medical follow-up (adjusted OR = 1.54) also influenced the level of diabetes knowledge. Acceptable glycemic control (adjusted OR = 4.20) was a factor in the development of good attitudes about diabetes.

Discussion

Identification of factors influencing the level of diabetes knowledge and attitudes is an integral part of educational diagnosis. These factors must be taken into account when establishing a personalized therapeutic education program adapted to each patient.

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EP308

Predictors of the level of knowledge, attitudes and quality of life of tunisian diabetics

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Objective

This study aimed to translate into Arabic and validate the questionnaires "Simplified Diabetes Knowledge Scale" (SDKS), "Diabetes Attitude Scale-3" (DAS-3) and "Diabetes Health Profile-18" (DHP-18) and to study the predictive factors of the level of knowledge, attitudes and quality of life of diabetics in the health region of Sousse.

Population and Methods

A methodological study of psychometric validation was carried out to meet the objective of translation and validation of the questionnaires. A second cross-sectional study was conducted to achieve the main objective of the study. Type 1 and type 2 diabetics from the health region of Sousse, aged 18 years and older and able to read and understand a newspaper in literary Arabic were included. The instrument developed contained a section to collect demographic and clinical data from the patients. Subsequent sections contained the Arabic translated and validated versions of the SDKS, DAS-3 and DHP-18.

Results

Analysis of the responses to the three questionnaires from 333 diabetics produced valid and reliable Arabic versions. One thousand and seven diabetics were collated to study the predictors of the level of knowledge, attitudes and quality of life of diabetics. The level of diabetes knowledge was related to demographic factors: high school (adjusted OR = 2.23) and university education (adjusted OR = 3.55), urban habitat (adjusted OR = 2.49) stable employment (adjusted OR = 3.04) and clinical factors: type 2 diabetes (adjusted OR = 4.02), insulin therapy (adjusted OR = 4.14), prior therapeutic education (adjusted OR = 1.55), self-monitoring of blood glucose (adjusted OR = 2.67), and regular medical follow-up (adjusted OR = 1.54). The development of positive attitudes towards diabetes was related to acceptable glycemic control (adjusted OR = 4.20). The quality of life of diabetics was negatively influenced by age < 40 years (adjusted OR = 2.50), type 1 diabetes (adjusted OR = 1.91), duration of diabetes of more than 10 years (adjusted OR = 1.43) and low level of knowledge about the disease (OR = 1.71).

Conclusion

Valid and reliable Arabic versions of the SDKS, DAS-3, and DHP-18 were produced and are available to caregivers for the assessment of knowledge, attitudes,

and quality of life of diabetics. The identification of factors affecting these parameters can be used as a basis for the development of a therapeutic education program adapted to this population

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EP309

Bicycle Exercise and Lifestyle Intervention in Newly Diagnosed Diabetes - An interim analysis of the BELIFE Study

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Background/Introduction
Lifestyle adaptations are crucial in the treatment of type 2 diabetes. However, implementation is difficult and patients especially with high glucose levels receive most often medication as first-line treatment instead of intensive lifestyle changes. We hypothesized that a primary lifestyle intervention as first-line treatment for newly diagnosed type 2 diabetes compared to standard of care is didactic, safe and can achieve metabolic control alone.
Methods
62 Adult patients with untreated type 2 diabetes diagnosed within the last 2 years and HbA1c $\geq$ 7.5% will be included in the study if they are clinically stable. After inclusion, patients are randomized to either the intervention group or the control group. Control group receives standard-of-care. Patients in the intervention group are asked to perform a 30-minute bicycle exercise. Clinical parameters are collected and blood analysis is performed throughout the exercise. Afterwards, patients undergo an exercise program along with regular motivational coaching, nutritional and diabetes counseling. HbA1c and glucose are measured after 3 months, to determine whether the intervention was successful. Primary endpoint is achievement of metabolic control, defined as reduction in HbA1c below a certain threshold depending on initial HbA1c, without antidiabetic medication 3 months after study enrollment.
Results
We conducted an interim analysis with 16 patients. Attainment of metabolic control was similar in both groups, with 75% ($n=8$) of patients in the intervention group reaching metabolic control after 3 months, compared to 50% ($n=8$) in the control group ($P=0.6084$). Both groups showed a significant reduction in median HbA1c levels from baseline over 3 months, with a 34.5% reduction from 10.15% to 6.65% in the intervention group ($P=0.0078$) and a 25.9% reduction from 9.85% to 7.30% in the control group ($P=0.0234$). The initial educative bicycle exercise lowered median blood glucose from 12.2 mmol/l to 10.05 mmol/l ($P=0.0078$) after 30 minutes. No significant safety issues were reported.
Conclusion
Data from this interim analysis supports the hypothesis, that intensified lifestyle intervention without anti-diabetic medication is safe and at least as efficient at reducing HbA1c as conventional treatment in patients with new-onset type 2 diabetes, even for patients with severe metabolic decompensation with an HbA1c higher than 10%.

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EP310

Effectiveness of OneCare digital diabetes IMPACT care program in patients with type 2 diabetes mellitus: An open label randomized controlled trial protocol

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Background
People with Diabetes (PwD) experience many obstacles in diabetes management including, but not limited to lack of motivation, limited knowledge on diabetes self-management and treatment adherence issues. Diabetes mandates regular follow-ups for good glycemic control and manage complications. Internet and smartphones, have revolutionized digital health and hence by employing digital health and technology, better outcomes may be achieved; which is realizable in Indian context with a very high smartphone prevalence adding value to manage the burden of world's second largest population with diabetes. IMPACT program by OneCare is a personalised digital comprehensive care program for PwD providing holistic management of diabetes. Very little scientifically robust data is available for the plethora of available commercial diabetes apps in the country. The objective of OneCare IMPACT trial is to determine the effectiveness of IMPACT program on glycemic variability, glycemic and metabolic parameters, including medicine changes over the standard of care.
Methods/Design
The IMPACT trial is an Indian open label, multi-centre, randomized, controlled study. 120 patients with an established diagnosis of T2DM, aged 18-70 years, having a smartphone access will be randomly assigned to standard care versus IMPACT program over standard care. Blinded CGMs would be applied before and at the end of interventions in both the groups. OneCare program interventions are virtual, coach-interactive sessions delivered over 12 weeks. The interventions will include qualified CDE as health coach, yoga, physical training and emotional wellness sessions, and mobile app to log-in the blood glucose, diet plan/ meal pictures, exercise/step counts, sleep hours. Patients in the control group will receive standard of care, driven by diabetes educators, meted out by the centre. IMPACT is powered to expect an effect size of 0·8 (SD 2·1) mmol/l between two groups. The primary outcome analysis would be CGM metric variations (glycemic variability, time in range and mean amplitude of glucose excursions) . Secondary endpoints include changes in HbA1c, BMI, pulse rate and blood pressure. Change in medicine dosages, laboratory parameters (FPG, PPG, lipid profile, hsCRP) and hypoglycaemic events are further outcome parameters of interest.
Discussion
In light of paucity in studies looking at the efficacy of digital DSME programs in Indian population, the IMPACT trial would substantially contribute to the scientific evaluation of the efficacy of OneCare program in T2DM to provide evidence to encourage the usage. Clinical Trials Registry-India number: CTRI/2022/09/045748.

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EP311

Design of a Randomized Withdrawal Period Following Long-Term Administration of Diazoxide Choline Extended-Release Tablets to People with Prader-Willi Syndrome

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Background
PWS is a rare genetic neurodevelopmental disorder characterized by hyperphagia, obesity, hormonal deficiencies, and problem behaviors for which there is no approved treatment. DESTINY PWS (C601) was an international, placebo-controlled, Phase 3 study of DCCR (diazoxide choline) extended-release tablet in participants with PWS, age 4 and older with hyperphagia. C602 is a long-term, open label extension to C601. DCCR administration to participants with PWS in these studies resulted in significant improvements in hyperphagia, behavior, body composition and metabolic markers. Significant improvements in hyperphagia and PWS associated behaviors were observed in a comparison of results from C601 and C602 to data from a cohort of participants in a PWS natural history study.
Objective
In order to further confirm the effects of DCCR administration on hyperphagia and other endpoints in a controlled setting, a randomized withdrawal (RW) period has been initiated for participants enrolled in C602. All have received DCCR for more than 2 years. The goal is to supplement the currently available data with further controlled data to support a regulatory filing. Input into the design, conduct and analysis of the RW period were sought from patients and caregivers, clinicians and from the FDA.
Methods
Participants who are currently enrolled in C602 will be consented to participate in a 16-week RW period and will be randomized 1:1 to DCCR or placebo. Following completion of the RW period, participants will be eligible to enroll in a new open-label study (C614). Participants who do not consent to the RW period will be eligible to enroll in C614 following 16 weeks off treatment. The primary endpoint of the RW period is change from baseline in Hyperphagia Questionnaire for Clinical Trials total score. Secondary endpoints include the Clinical Global Impression of Improvement (CGI-I), and the Clinical Global Impression of

Severity (CGI-S). Each endpoint will be assessed at baseline (except CGI-I which measures improvement from baseline) and at 4, 8, 12 and 16 weeks. Additional endpoints include changes in other PWS-associated behaviors as assessed by the Prader-Willi Syndrome Profile Questionnaire, weight and BMI, a set of CGI-S of various PWS behaviors and assessments by the Caregiver Global Impression of Severity and Change. The Baseline and 16-week visit are in-clinic, all others are telemedicine. Safety monitoring will occur as it was in C602.

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EP312

Nutrition risk assessment in patients with Crohn disease

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Background
Malnutrition and weight loss are well-recognized complications of Crohn disease (CD), however nutritional routine assessment is not commonly performed, resulting in under-detection and under-treatment of both malnutrition and nutrient deficiencies. In fact, a number of nutrition screening tools are available including the Nutritional Risk Index (NRI).
Aim
The aim of this study was to investigate the prevalence and the associated factors of malnutrition during CD.
Methods
We conducted a retrospective single-center study, including patients followed for CD over a 7-year period [2014 - 2021]. Clinico-biological data, anthropometric data, disease severity, and long-term outcomes were collected. Malnutrition risk was estimated based on Nutritional Risk Index (NRI) calculated at first presentation with the following formula: NRI = (1.519 × serum albumin (g/L) + 41.7× (present weight/usual weight). Nutrition status of patients was categorized into four groups: NRI score of > 100 was considered in no risk group, 97.5–100 mild risk, 83.5–97.5 moderate risk, and < 83.5 severe risk group.
Results
In total, 50 patients were enrolled with a mean age of 44.3 years [20-82], a median disease duration of 106 months and a sex ratio M/F of 3.16. Based on NRI, 11/50 (22%) patients had normal nutritional status, 27/50 (54%) mild-moderate risk of malnutriton and 12/50 (24%) had severe malnutrition. In the univariate study, severe malnutrition was associated with the presence of anemia ($P=0.002$), thrombocytosis ($P=0.05$), hypocholesterolemia ($P=0.024$), as well as the existence of radiologic sarcopenia ($P=0.05$). This risk was increased by extensive ileal involvement of more than 50 cm ($P=0.014$), the occurrence of complications such as intraabdominal collection ($P=0.001$) and thromboembolic complications ($P=0.05$). Uncontrolled disease in severe relapse was also a factor associated with malnutrition ($P=0.05$). Regarding, patients who underwent surgical treatment, the occurrence of postoperative complications and extensive small bowl resection were factors associated with severe malnutrition with a *P*-value of 0.02 and 0.025 respectively. On multivariate regression analysis, patients developing intra-abdominal abscess were more likely to have malnutrition (OR 10.5 95% CI 2.22-49.51), $P=0.003$).
Conclusion
Patients with malnutrition had more severe course of CD. Nutritional Risk Index is a simple, validated and reproducible tool to identify patients at increased risk of malnutrition allowing adapted nutritional support.

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EP313

Is the concentration of ghrelin and leptin important for the course of COVID-19 infection?

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Objectives
SARS-Cov2 infection can lead to severe cytokine storm especially in obese patients. It is known that the cytokine storm might lead to severe clinical manifestations or even acute mortality in critically ill patients with COVID-19. Ghrelin as well as leptin can act as the proinflammatory cytokines. The essential question is whether the cytokine storm in COVID-19 patients with obesity is associated with adipokines dysregulation.
Aim
The study aimed to assess ghrelin and leptin concentrations in patients 6 months after the SARS-Cov2 infection in comparison to control group. In addition, selected biochemical, hormonal, anthropometric and densitometric parameters, considering the influence of sex, were also assessed.
Material and Methods
The study group included 53 patients with a history of COVID-19 and 87 healthy subjects in the control group. Leptin and ghrelin concentrations as well as hormonal and biochemical were measured. The bioethics committee of Wroclaw Medical University approved the protocol of the study. All subjects signed informed consent forms in line with the Declaration of Helsinki. The statistical analysis was performed using R for Windows statistical software (version 4.0.4, Vienna, Austria).
Results
A statistically higher ghrelin concentration was observed in the COVID-19 group in comparison to the control group (1190.56 pg/ml vs 901.39 pg/ml, $P=0.003$), with statistically significant impact of the sex on the relationship between COVID-19 and ghrelin concentration which was lower in males. No statistically significant differences in leptin concentration were observed between the groups although in both groups we observed significantly lower leptin level in males ($P=0.033$). Significant negative correlation was observed between ghrelin and testosterone and morning cortisol levels in COVID-19 group. We observed significant correlation between leptin concentration and metabolic parameters as well as CRP levels in both groups.
Conclusions
The higher levels of ghrelin in patients with mild form of SARS-Cov2 infection for up to six months ago might indicate the possible protective role of ghrelin in inflammatory process. In our study leptin levels did not differ between both groups of patients, probably because patients had only slightly increased BMI. We could also suppose that leptin might be involved in the dysregulation of proinflammatory cytokines in obesity, which is the leading cause of high morbidity and mortality in patients with SARS-CoV-2 infection.

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EP314

The effect of olfactory odour stimulation on serum oxytocin levels and glucose metabolism: Data from the OLFAMET study

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Background
Studies in rodents and non-human primates revealed beneficial effects of oxytocin on systemic metabolism, body weight and food intake. Several rodent studies demonstrated that olfactory stimulation with D-limonene, improves systemic glycemia, reduces food intake and body weight, while olfactory stimulation with the scent of lavender oil had opposite effects. The aim of this study was to investigate if systemic oxytocin levels are affected upon olfactory stimulation with D-limonene and lavender oil, compared to placebo, in obese humans.
Methods
Single-centre, randomized, cross-over trial with $n=$ 40 participants of both genders, age 18-60 years, with a body mass index (BMI) $\geq$ 35 kg/m^2. Only participants with normosmia (as defined by Sniffin' Sticks Test and threshold, discrimination and identification (TDI) score) and absence of co-morbidities were included. Participants were stimulated with D-limonene, lavender oil and placebo (propylene glycol, all from Sigma Aldrich) for 15 minutes in a randomized cross-over fashion and a wash-out period of 1 week between treatments. After olfactory stimulation, participants received a calorie- and carbohydrate-rich mixed meal test, and blood glucose was measured at 0, 5, 15, 30, 60, 90, 120 minutes. Oxytocin levels were measured via an ELISA kit before and directly after olfactory stimulation with the different odours.
Result
The study included 40 subjects (12 males, 28 females) with a median age of 38.5 [28: 50.5] years and a median BMI of 38.1 [36.2: 42.5] kg/m^2. There was no

difference in oxytocin plasma levels before and after olfactory stimulation with D-Limonene or lavender oil vs placebo (delta (Δ) for D-limonene -2.23 [-14.84: 13.64] pq/ml ($P=0.696$), Δ lavender oil 0.35 [-15.33: 16.38] pq/ml ($P=0.804$) and Δ placebo 2.71 [-8.15: 14.29] pq/ml ($P=0.455$). Participants were divided into subgroups by BMI (< 40 kg/m^2 vs ≥ 40 kg/m^2) and further by gender. The only subgroup with an increase in plasma oxytocin were men with a BMI < 40 kg/m^2 upon olfactory stimulation with D-limonene (Δ 14.73 [2.45: 34.04] pq/ml (0.036*)), while neither changes were seen upon lavender oil (Δ - 7.24 [- 18.60: 2.28] pq/ml ($P=0.093$)) or placebo (Δ 3.75 [-10.36: 18.45] pq/ml ($P=0.779$)) nor in the other subgroups.

Conclusion

Acute olfactory stimulation with D-limonene increases plasma oxytocin levels exclusively in men with BMI < 40 kg/m^2. Thus, metabolic effects upon olfactory D-Limonene treatment do not seem to be related to changes in systemic oxytocin.

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EP315

Levothyroxine dosing following bariatric surgery – A 4-year follow up

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Introduction

The anatomical and physiological changes induced by bariatric surgery (BS) can significantly impact the absorption and pharmacokinetics of orally administered medication. In particular, levothyroxine (LT4) dosage, given its dependence on patient's weight and gastric pH for optimal absorption, is expected to change following BS. However, the literature is not unanimous and there is a void of longer-term studies. We aimed to compare LT4 dosage 4 years following BS, comparing malabsorptive versus restrictive techniques.

Methods

This was a retrospective observational study performed in a single center between 2010 and 2017 that included patients that underwent BS (Roux-en-Y gastric bypass (RYGB) and gastric sleeve (GS) and completed a 4-year follow up. All hypothyroid patients under LT4 ($n=86$, 92% female, age: 48 ± 11 years, BMI: 43.1 ± 4.3 kg/m^2) were selected from a total of 1070 patients (8%). GS was performed in 39 (45.3%) and RYGB in 47 (54.7%). 44 patients had autoimmune thyroiditis (AIT), 33 had thyroid resection, 3 had central hypothyroidism, 6 unclarified etiology.

Results

Four years after surgery, 23 (59%) patients that underwent GS and 22 (46.8%) that underwent RYGB required a lower daily dose of LT4, had to be increased in 6 (15.4%) and 10 (21.3%) and remained unchanged in 10 (25.6%) and 15 (31.9%), respectively. No statistically significant differences were found between types of surgery. For both GS and RYGB we observed statistically reduced values of total daily dose of LT4 at years 1 and 4 when compared to baseline ($P<0.001$), while the average weight-based daily LT4 was significantly increased at years 1 and 4 when compared to baseline (1.31 μg/kg (± 0.55) at baseline, 1.48 μg/kg (± 0.51) at year 1 and 1.42 μg/kg (± 0.55) at year 4 for GS; 1.11 μg/kg (± 0.44) at baseline, 1.47 μg/kg (± 0.55) at year 1 and 1.41 μg/kg (± 0.47), $P<0.001$). In pairwise comparisons, doses at year 1 and 4 are not statistically different. The same pattern was found independently of hypothyroidism etiology.

Conclusion

Our results are consistent with previous work, demonstrating that following BS, individuals with hypothyroidism and obesity frequently require a lower dose of LT4 per body weight. We further demonstrate that this trend is sustained for at least 4 years. Nevertheless, there is variability, with some patients requiring dosage increment or no adjustment, highlighting the importance of tight and individualized monitorization of patients with hypothyroidism after BS.

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EP316

Pain in lipedema: proposal for clinical evaluation and correlation with clinical aspects, anthropometric measurements and hormonal profile

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Aim

Lipedema is a **painful** fat disorder that affects 11-17% of woman. The diagnosis is based on typical clinical features: bilateral symmetrical disproportionate fatty tissue hypertrophy on the limbs sparing of the hands and feet, feeling of heaviness and tension, easy bruising, transient edema and pain in the affected areas. There are three clinical stages (1, 2 and 3) that refer primarily to appearance of the skin, texture of subdermal tissue and the presence of palpable nodules and fat accumulation. The clinical severity of the disease increases with the stage. The pain is a fundamental diagnostic element but it is not one of the criteria used for staging, it is very variable and a specific and comparable score to quantify it has not yet been validated. The aim of the study was to evaluate the correlation between the pain by pinching the subcutaneous tissue of the lower limbs with clinical history, anthropometric measurement and laboratory tests.

Materials and Methods

70 women with lipedema underwent clinical evaluation and blood tests. we measured the pain by pinching a skin fold in 6 points of the lower limbs applying a scale from 0 to 4 (0= no pain, 4= maximum pain). the total score ranges from 0 to 24.

Results

All patients had pinch pain, with a total score of 12-24 (mean 19.11 ± 3.57). Based on the clinical stage, we found: 37.1% with stage 1, 38.6% with stage 2 and 24.3% with stage 3. Age, years since disease onset and BMI increase progressively with the clinical stages ($P=0.031$, $P=0.005$, $P=0.000$ respectively). There were no significant differences in the pain score between the 3 clinical stages. There are no significant correlations with white blood cell count, CRP, glucose metabolism indices, estradiol, progesterone, androgen, IGF-1, TSH, FT3 and FT4 levels. The pain score does not correlate with age, disease duration, BMI, waist and hip circumference, WHR or with WHrT. The pain score correlates positively with a single anthropometric parameter: the ratio between hip circumference and height.

Conclusion

The clinical staging currently used for lipedema does not correlate with the pain. Pain should be systematically assessed with a specific score and should be included in the criteria for assessment of clinical severity or staging. The ratio between hip circumference and height, as a new anthropometric index, could be an interesting index for the clinical evaluation of the patient affected by lipedema.

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EP317

Using Morisky scale to measure adherence and factors associated with non-adherence in patients with type 2 diabetes mellitus: A systematic review

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Aim

We conducted a systematic review aiming to:

- Measure self-reported adherence to medication in patients with type 2 diabetes mellitus (T2DM) using the Morisky medication adherence scales (MMAS).
- Identify barriers and facilitators associated with adherence.

Methods

The systematic review was conducted in accordance with the PRISMA Framework and was registered with PROSPERO (CRD42022359969). The Medline, Embase, Emcare and Ovid Nursing database were searched with predefined keywords and search strategy between the period of 2013 and 2022. Studies were included within the current review if they were cross-sectional and used the MMAS to measure adherence to medication in patients with Type 2 Diabetes (T2DM). Double-blinded screening was used to minimise the risk of bias. Inclusion criteria for participants in the studies were: adults $>$ 18 years, diagnosed with T2DM and prescribed anti-glycaemic medications, including insulin. A narrative synthesis was adopted for data analysis to report factors that influenced nonadherence and MMAS adherence scores. Deductive thematic analysis utilising the COM-B Behavioural change model was used to map identified barriers and facilitators to adherence against the Capability, Opportunity and Motivation.

Results

Of the 9,990 returned records, 30 studies from 17 countries and with a total of 8,402 participants across all studies were analysed. Three studies found that $>80\%$ of their participants had high prevalence of adherence; in 15 studies participants reported high level of adherence to medication, in 3 studies participants had medium level and in 12 studies participants had low adherence to medication. The average level of high adherence was 40.93% and low adherence 42.64%, highlighting most study participants had a low level of medication adherence. Most common patient-level barriers to adherence included depression and poor diabetes knowledge, polypharmacy and healthcare related cost.

Conclusions
The MMAS scale is a reliable tool to measure self-reported adherence and yield homogenous results across studies. Adherence to medication remains low. A greater identification of diabetes-related depression, fewer medication, structured diabetes education programmes and a greater awareness of barriers by health care professionals can contribute to effective behavioural changes that could positively influence adherence to medication.

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EP318

Atezolizumab induced new-onset type 1 diabetes mellitus and thyroiditis

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Introduction
Cancer is the result of genetic and epigenetic alterations generating uncontrolled cell growth. These molecular changes maintain an immunosuppressive microenvironment allowing tumor spread. Immune checkpoint inhibitors (ICI) are novel therapeutic strategies in cancer treatment, promoting anti-tumor response by boosting cytotoxic T lymphocytes. Despite their high effectiveness, they can trigger the activation of diverse autoimmune diseases in genetically predisposed individuals. New-onset autoimmune Diabetes Mellitus type 1 (T1D) is an extremely unusual side effect, described in less than 1% of patients.
Materials and Methods
A case report description conducted with the consent of the patient and with provisions of the Declaration of Helsinki.
Results
Here we present a 44-year-old male with a medical history that includes chronic hepatitis C virus infection, and paranoid schizophrenia. No personal or familial diagnosis of diabetes. He had recently been diagnosed with hepatocarcinoma, presenting retroperitoneal and hepatic hilar adenopathy, making the tumor unresectable. After the onset of ICI, he was diagnosed of two PD-L1 inhibitor-induced autoimmune endocrinopathies, presented as diabetic ketoacidosis (DKA) and thyroiditis. After two cycles of atezolizumab and bevacizumab, he consulted the emergency department with abdominal pain and diabetes cardinal features (polyuria, polydipsia, vomiting). Blood tests demonstrated hyperglycemia superior to 800 mg/dl, capillary ketonemia >3 mmol/l, metabolic acidosis (pH 7.24 with HCO3- 14 mEq/l). Subsequent studies detected a low level of C-peptide level 11 pmol/l, and positive glutamic acid decarboxylase and insulinoma-associated antigen-2 antibodies. Thyroid examination was compatible with thyroiditis, showing a high free thyroxine level (1.91 ng/dl) with low thyrotropin (0.08 mIU/l), negative anti-peroxidase, and anti-TSH receptor, and slight positivity of antithyroglobulin antibodies. After reaching metabolic stabilization, treatment with Atezolizumab was restarted, with no further complications.
Conclusion
Monoclonal antibody targeting has become a breakthrough, generating a shift in the treatment of advanced malignancies. These new drugs promote an anti-tumor immune response. Nevertheless, immune checkpoint blockade is associated with a risk for immune-related adverse events in genetically predisposed individuals. T1M related to ICI is a rare condition that presents as a life-threatening emergency and should be recognized and treated early. Blood glucose and Hb1Ac determinations should be performed at periodic visits for detection. There are genetic factors that predispose susceptible individuals, but there is no evidence of studies to be performed before the onset of ICI or preventive strategies.

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EP319

Leptin reduces the risk of poor glycemic control in type two diabetes mellitus patients on metformin therapy

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Purpose
Type two diabetes mellitus (T2DM) is a chronic disease of debilitating complications. Good glycemic control could delay disease progression and microvascular complications. Nonetheless, some patients cannot maintain glycemic control.
Patients and Methods
We recruited 340 T2DM patients on metformin therapy and categorized them according to their HbA1c levels into patients with good vs poor glycemic control. The levels of serum leptin were measured. Patients were genotyped for the following SNPs in the *LEP* gene (rs7799039, rs2167270 and rs791620).
Results
Serum leptin reduced the risk of poor glycemic control following adjustments with age, gender, BMI, treatment duration and HOMA-IR (OR = 0.984; CI: 0.973 - 0.994; $P=0.002$). The GA genotype of rs2167270 was less frequent in patients with poor glycemic control and reduced its risk in multivariate analysis (OR = 0.428; CI: 0.248 - 0.737; $P=0.002$).
Conclusion
These findings suggest that leptin therapy or strategies that re-sensitize tissues to existing leptin could be utilized for better glycemic control in T2DM patients on metformin.

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EP320

Implementation of the use of MFG in Antequera Hospital (Spain)

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Introduction
Poor metabolic control in type 1 diabetes mellitus (T1DM) is associated with micro and macrovascular complications. The implementation of interstitial glucose monitoring systems has contributed to the improvement of glycemic control in recent years.
Objectives
Our main objective was to analyze the results of implementing flash glucose monitoring (FGM) devices after 1 year, and see if it managed to improve glycemic control in our patients.
Material and Methods
Cross-sectional observational study in people with T1DM, carriers of the FGM devices, with follow-up at Hospital of Antequera (Malaga, Spain) during the first year since the establishment of a specific medical consultation. We collect the HbA1c prior to the start of FGM, HbA1c a year after FGM, average glucose, time in range, and glucose management indicator (GMI). The analysis has been carried out using the JAMOVI program.
Results
154 patients were included, 41.2% women, mean age 40.8 ± 14.7 years, mean evolution time 18.9 ± 11.5 years, 18.9% presented diabetic retinopathy, 15.5% presented diabetic neuropathy, 27% presented high blood presure, 39.2% associated dyslipidemia. The HbA1c prior to the use of FGM is 8.13% and one year after the use of FGM is 7.65% ($P<0.01$). The average glucose from the FGM is 170 ± 47.6 mg/dl, variability 36.6 ± 8.22%, GMI 7.33 ± 1.34%, time-in-range (TIR) 54.8 ± 21.1%, reaching a TIR above 70% in 27.5% of the patients, use of the sensor of 86.2 ± 18.6%.
Conclusions
The use of FGM has improved glycemic control in people with T1DM being followed up at the Endocrinology consultation at the Hospital of Antequera.

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EP321

Clinical features of the course of various types of diabetes mellitus in young people

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The age group under 45 years is the most difficult to determine the type of diabetes mellitus (DM), it can include type 1 (DM1), type 2 (DM2), MODY and LADA diabetes. Objective of the study: to determine clinical markers for differential diagnosis of types of DM in young patients.

Materials and Methods
202 patients with onset of diabetes aged 18 to 45 years were included: group 1 - 77 patients with MODY, 2 - 83 with DM 2, 3 - 14 with DM 1, 4 - 28 with LADA. The groups were comparable in terms of gender and age. Patients were compared according to aggravated heredity for DM, features of the onset of the disease, comorbid pathologies and baseline anthropometric parameters.
Results
Patients with MODY more often than with DM2, with DM1 and LADA had a burdened heredity for DM (95 and 79%, $P=0.005$, 95 and 29%, $P<0.001$, 95 and 64 $P=0.035$), more often relatives developed DM up to 45 years (70 and 29%, $P<0.001$, 70 and 14%, $P<0.001$) and more than in 3 generations (65 and 28%, $P<0.001$, 65 and 7%, $P<0.001$, 65 and 8%, $P<0.001$, 65 and 15%, $P<0.001$). Patients with DM2 had often than with MODY obesity (34 and 4%, $P<0.001$), diseases of the gastrointestinal tract (25 and 6%, $P=0.001$) and arterial hypertension (14 and 5%, $P=0.044$). Patients with DM1 had more often than in MODY and DM2 symptoms of DM (93 and 23%, $P<0.001$, 93 and 26%, $P<0.001$), weight loss (50 and 3%, $P<0.001$, 50 and 0%, $P<0.001$), ketoacidosis (64% and 1%, $P<0.001$, 64% and 1%, $P<0.001$). In DM1, ketoacidosis was more common than in LADA (64 and 15%, $P=0.013$). In LADA more often in DM2 were symptoms of DM (61 and 26%, $P=0.016$), weight loss (15 and 0%, $P=0.017$) and less often gastrointestinal tract diseases (0 and 25%, $P=0.031$). With LADA more often than with MODY were symptoms of DM (61% and 23%, $P=0.009$), obesity (31% and 4%, $P=0.008$) and thyroid pathology (31% and 9%, $P=0.040$).
Conclusion
Clinical characteristics for differential diagnosis of the type of DM are aggravated heredity for DM, weight of patients; the presence of clinical symptoms, ketoacidosis in the debut; the presence of arterial hypertension, concomitant diseases of the gastrointestinal tract and thyroid gland.Acknowledgements: Abstract was written of the grant of the President of the Russia for state support of young Russian scientists - doctors of sciences MD-3017.2022.3.

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EP322

Long-term glycaemic follow-up results of hospitalised COVID-19 patients with hyperglycemia

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Introduction and Aims
A higher prevalence of hyperglycemia has been reported in patients affected by coronavirus disease 2019 (COVID-19). Our study aims to retrospectively evaluate the course of hyperglycemia in patients recovering from COVID-19.
Methods
All patients who were hospitalised in Çanakkale Onsekiz Mart University Hospital between March 2020 and March 2022 due to COVID-19 and whose HbA1c values were checked during hospitalisation were examined. Chronic kidney damage, oncological diagnosis, and pregnancy were determined as exclusion criteria. Three hundred twenty-four patients who met the current conditions were included in the study. Patients were followed up 3-12 months after hospitalisation.
Results
A total of 324 patients with a mean age of 67.48 ± 12.36 years, including 151 (46.6%) women, were included in the study. It was determined that 191 (59%) of 324 cases were still alive, and the number of deceased was 133 (41%). Patients with known DM had significantly increased glucose and glycated hemoglobin (HbA1c) values before and during hospitalisation (glucose 167 (IQR: 129-222) vs 225 (IQR: 162-329) mg/dl, $P<0.001$) (HbA1c 7.8 (IQR: 7.0-9.75) vs 8.5 (IQR: 7.3-10.55), $P<0.001$). A significant decrease was observed in glucose and HbA1c values measured during hospitalisation and in the last outpatient clinic controls of known DM patients (glucose 225 (IQR: 162-329) vs 164 (IQR: 126-232) mg/dl, $P<0.001$) (HbA1c 8.5 (IQR: 7.3-10.55) vs 7.9 (IQR: 6.7-9.03), $P<0.001$). When 163 patients from known diabetic patients who came to the outpatient clinic were evaluated, it was observed that the treatment did not change in 83 (50.9%) patients, it was intensified in 67 (41.1%), and the treatment was reduced in 13 (8%). A significant decrease in glucose and HbA1c levels was observed compared to baseline in known diabetic patients who did not change treatment during follow-up (glucose 204 (IQR: 152-303) vs 165 (IQR:117-227) mg/dl, $P=0.001$) (HbA1c 8.35% (IQR: 7.1-10.1) vs 7.8% (IQR: 6.6-8.8), $P=0.001$).
Conclusion
In our study, it was observed that in hospitalised diabetic COVID-19 cases, the level of hyperglycaemia at admission decreased during follow-up. In our patients whose anti-diabetes treatment did not change, regression was observed in hyperglycaemia with the recovery of the infection. Prospective studies of the finding's evaluation will provide more precise evidence.

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EP323

Programmed cell death-1 inhibitor-induced Type 1 Diabetes Mellitus – an interesting case presenting with diabetic ketoacidosis

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Introduction
Immunotherapy has demonstrated a key role in the current individualized treatment of multiple neoplasms, with adverse events related to the endocrine. Thyroid dysfunction is the most frequent reported endocrine event during treatment with pembrolizumab, being autoimmune diabetes an extremely rare adverse effect.
Case Report
We present a case of a 72-year-old man with a progressing urothelial bladder carcinoma (stage IIIB), under treatment with pembrolizumab since 2018. He had the diagnosis of primary hypothyroidism four months after starting the treatment, no personal or family history of diabetes mellitus, and his usual fasting plasma glucose levels were 102-113 mg/dl in the last six months. He was admitted in 2022 due to abdominal pain, anorexia, polydipsia, polyuria, nausea and vomiting with one week of evolution after performing contrast-enhanced imaging, with criteria for severe diabetic ketoacidosis (DKA) (pH 7.18, HCO3 2.9 mEq/l, glucose 695 mg/dl, ketonemia 7.3 mmol/l). He was medicated with prednisolone 20 mg/day three days before admission, due to suspected contrast hypersensitivity reaction. During hospitalization, he underwent fluid therapy with KCl supplementation and intravenous insulin infusion, having transitioned to a basal-bolus scheme after DKA resolution, with progressive glycemic stabilization. Further investigation revealed undetectable levels of C-peptide (0.07 ng/ml), HbA1c 9.2% and positive islets autoimmunity (positive anti-IA2 antibodies), which allowed the diagnosis of autoimmune diabetes. The drug was transiently suspended, and the patient resumed treatment after glycemic profile optimization under insulin therapy.
Conclusion
This clinical case highlights the importance of clinical suspicion and glycemic monitoring in addition to thyroid function, as an integral part of treatment protocols in patients on pembrolizumab and other immune checkpoint inhibitors. In the presence of autoimmune diabetes, the need for long-term insulin therapy is invariably necessary, with the possibility of resuming the drug after adequate glycemic stabilization.

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EP324

Micronutrient deficiencies and functional disorders of postmenopausal diabetic women

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Aim of the study
Functional disorders might be caused by micronutrient deficiencies. The objective of our study is to screen the micronutrient deficiencies of postmenopausal diabetic women and determine their impact on the functional disorders.
Methods
This is a cross-sectional descriptive study made within the National Institute of Nutrition of Tunis, including 55 postmenopausal diabetic women which benefited from a dietary survey. Functional disorders were detected by the Screening of Micronutrient deficiency (DDM) questionnaire that allows to classify these disorders and evaluate the different disruptions.
Key findings and Results
The average age of our patients is of 63.7 ± 6.5 years old. The dietary survey showed an insufficiency intake of vitamins A, D, C, E, B6, B9, and B12 for respectively 35%, 60%, 38%, 49%, 53%, 34% and 52% of cases. Additionally, insufficiencies of magnesium, iron and zinc intake were observed, for respectively, 49%, 40% and 64% of cases. We found negative and statistically

significant correlations between fatigue, mood disorders and vitamin C (r=-0.297, P=0.028), magnesium (r=-0.441, P=0.01), and iron (r=-0.458, P < 0.01), between digestives troubles and fiber intake (r=-0.458, P <0.01), between osteoarticular disorders and degenerative diseases and vitamin A intake (r=-0.422, P=0.01) as well as manganese (r=-0.287, P=0.03), and finally between circulatory system diseases and vitamin C (r=-0.294, P=0.03).
Discussion
A suitable micronutrient approach for each of our patients is mandatory to maintain an optimal health and correct the functional disorders.

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EP325

Quality of life and associated factors in a Tunisian diabetic population

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Objective
Our objective was to assess quality of life (QoL) in a diabetic population and to identify factors associated with its deterioration.
Patients and Methods
This was a cross-sectional study of 100 type 1 or 2 diabetic patients followed up at the outpatient department of the National Institute of Nutrition in Tunis. The QoL was evaluated using the questionnaire "Diabetes Quality of Life" (DQoL) validated in Arabic version. The latter is a score composed of 29 items divided into 3 factors: concern, impact and satisfaction. It is positively correlated with an impaired QoL.
Results
The mean age of the population was 55.9 ± 13 years with a female predominance in 2/3 of the cases (67%). The majority were type 2 diabetics (89%). The age of diabetes was 14.3 ± 9.35 years. Degenerative complications were observed in 61% of the patients. Three quarters (74%) were on insulin therapy. The mean hbA1c was 11.5 ± 1.8% with an out-of-target level in 66% of cases. Diabetic imbalance was mainly due to dietary deviation (89%). Poor adherence to treatment was noted in a quarter of the population (25%). The mean DQoL score was 85.2 ± 13.6. This score was higher in the female population but not significantly so (P=0.31). It was significantly higher in type 2 diabetics compared to type 1 diabetics (P=0.019). Unbalanced diabetes and the presence of degenerative complications were significantly associated with a deterioration of the QoL (P<0.001 and P=0.031 respectively). The DQoL score was also higher in insulin-treated diabetics but not significantly so (P=0.37). Higher education and medication adherence were associated with better QoL (P=0.23 and P<0.001 respectively).
Conclusion
This study demonstrates the impact of several factors, including diabetes imbalance, the presence of degenerative complications, and educational level, on the QoL of diabetic patients. Therefore, the improvement of this parameter requires therapeutic education and a global management of this chronic pathology.

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EP326

Increased Knowledge and Awareness about Endocrinology and Science-based Careers Amongst School Children through Public Engagement Event

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Background
It is important to engage and encourage young adults from all economic backgrounds to pursue a career in science and medicine to create an equitable society. Several awareness campaigns are currently underway to improve the awareness and knowledge of various metabolic conditions to promote good lifestyle practices in adolescents. However, such opportunities do not seem to reach those from deprived areas. We conducted public engagement events on students' attitudes towards science-related careers and knowledge and perceptions regarding diabetes, polycystic ovary syndrome (PCOS), health technology, and obesity in deprived areas. In this study, we report the impact of such interventions.
Methods
A half-day public engagement event was held in two state secondary schools in deprived areas of Birmingham in July 2022. Students aged 14-16 years were invited to attend the sessions. The event included three pre-recorded lectures on obesity and diabetes, PCOS and health technology. Following the lecture, all participants worked in groups of 5-8 to make posters showcasing what they learned during the session. This was followed by a speed-dating session with professionals in various science fields so students can find out more about how to get into science-related careers. All participating students completed pre- and post-session surveys. Responses were quantitatively analysed using Wilcoxon Signed Rank. Thematic analysis was conducted on the posters to identify themes as understood by students.
Results
Students had an increased understanding of diabetes (+24.5%, P<0.001), obesity (+15.0%, P=0.007), PCOS (+65%, P<0.001) and emotional well-being (+16.2%, P=0.003), and a better understanding of a career as a scientist (+28.4%, P<0.001). Students also had an increased understanding of what a career as a doctor entailed and an increase in the proportion of students who said they would be interested in a career in health science; however, these were not statistically significant (+1.9%, P=0.904 and +4.9%, P=0.519 respectively). The majority of students found interacting with healthcare professionals informative, and 40% of students said they are likely to do further reading regarding healthcare careers. Within the PCOS and diabetes posters, the main themes identified included the pathophysiology, symptoms and management of each condition as well as the differences between type 1 and type 2 diabetes. The overarching themes of the health technology posters were of health technology at an individual level and within the healthcare system.
Conclusions
Public engagement activities can change attitudes towards science-related careers, enhance understanding of medical conditions and perceptions of these conditions in students.

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EP327

Precipitating factors of diabetic ketoacidosis before and during COVID-19 pandemic

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Introduction
COVID-19 has been incriminated directly and indirectly in the increase of patients presenting with diabetic ketoacidosis.
Aim
The aim of this study is to compare diabetic ketoacidosis precipitating factors in the pre-pandemic and during the pandemic.
Methods
This is a retrospective comparative study between patients hospitalized in the diabetology department in the university hospital Farhat Hached of Sousse for diabetic ketoacidosis in the pre-pandemic (between March 2018 until March 2020) (G1) and during pandemic period (between March 2020 until March 2022) (G2).
Results
A total of 340 patients were included in this study, with 137 patients admitted in the pre-pandemic period (G1) and 203 admitted during pandemic period (G2). The overall distribution of diabetic ketoacidosis precipitating factors differed significantly in the pre-pandemic compared to the pandemic period (P=0.028) with a significant increase of psychological stress (31.2% in G2 vs 22.4% in G1 with an adjusted residual (AR) of 1.98) and excessive food intake notably hypertonic drinks (6.5% vs 2.2%, AR=2) at the expense of corticosteroid use as its accountability in precipitating DKA significantly decreased in G2 (1.5% in G2 vs 6.5% in G1, AR=2.2). In contrast, overall infections accountability did not differ between the two groups (28.6% in G2 vs 29.1% in G1, AR=0.1). The same was noticed regarding cardiovascular events. No identifiable precipitating factor was found in 40.3% in G1 vs 31.7% in G2 (AR=1.6). More specifically, infectious precipitating factors had a significantly different distribution between

the two groups ($P<0.001$) with COVID-19 becoming the first infectious precipitating factor of DKA in G2 (37.04% vs 0% in G1, AR = 4.2) with a decrease of pulmonary and other influenza like illness. The accountability of cutaneous, urinary, profound and other specific infections remained the same in the two groups with a respective AR of 1.8, 0.6, and 0.9.
Conclusion
COVID-19-like any other infection- is directly responsible for triggering diabetic ketoacidosis. COVID-19 seems to decompensate diabetes also indirectly through different mechanisms with an increased accountability of psychological stress and excessive food intake as precipitating factors due probably to periods of lockdown and restricted social activities. The accountability of corticosteroid use seems to decline as most of patients in this study who developed COVID-19 had minor symptoms and therefore did not require corticosteroids.

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EP328

Dynamics of HbA1c and glycemia in OGTT during pregnancy in healthy women

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Introduction
Some physiological changes in HbA1c during pregnancy should be considered to determine its optimal value for glycemic control. Erythrocytes half-life decreases during pregnancy, which is reflected in a decrease in HbA1c.
Aim
The aim of this study is to analyse HbA1c during pregnancy in healthy population of pregnant woman. Matherial and methods: The study included 77 pregnant women in the first trimester registered in Center for endocrinology UCC Kragujevac that were tested using OGTT, according to ADA criteria: pregestational and gestational diabetic women were excluded, and also determinaning thyroid parameters (fT4, TSH, TPOAb). We analyzed the HbA1c values of 46 healthy pregnant women (without gestational diabetes mellitus and thyroid disorders including autoimmune thyroiditis). The characteristics of the participants were expressed as mean ± standard deviation.
Results
The mean age of 46 healthy pregnant women was 29.4 ± 4.5 years It has been shown that the normal range of HbA1c was 4.97-5.14% in early pregnancy, and 5.09-5.34% in late pregnancy (Table).
Conclusion
This study demonstrates that the reference range of HbA1C in healthy pregnant women during pregnancy was 4.97% to 5.34% in our population.
Keywords: HbA1c, OGTT, pregnancy

HbA1c (%)	1.trimester	2. trimester	3. trimester	After delivery
X ± SD	5.05 ± 0.28	5.03 ± 0.37	5.08 ± 0.13	5.22 ± 0.43
(95%CI)	(4.97-5.14)	(4.92-5.14)	(4.98-5.17)	(5.09-5.34)

glycemia during OGTT(*mmol/l*) (*min-max*)	1.trimester	2. trimester	3. trimester	After delivery
0. min	4.0-4.78	3.6-4.56	3.43-4.37	4.15-4.95
60. min	4.3-7.26	4.95-7.99	5.77-8.43	
120. min	4.04-6.12	4.23-6.59	5.27-7.49	4.16-6.16

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A case series of monogenic diabetes in pregnancy

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Monogenic diabetes is estimated to account for 1-2% of all diabetes cases diagnosed before the age of 45. It is caused by mutations in genes encoding for beta cell development, function and regulation. We present three cases of monogenic diabetes in pregnancy.
Case 1
Age 30, Para 3, White ethnicity. This individual was screened for a GCK mutation at 18 weeks gestation (third pregnancy) on the basis of family history. She required metformin and insulin to maintain glycaemic control. Fetal birth weight (FBW) measured 3.7 kg at 39 weeks' gestation. Post-partum, the mutation was confirmed in the mother: she has mild persisting fasting hyperglycaemia.
Case 2
Age 40, Para 3, Turkish. This case represents a known homozygous HNF1A mutation. Insulin requirements increased during pregnancy. Delivery was expedited (concerns regarding pre-eclampsia) and her baby measured 2910 g at birth (37 + 2 weeks' gestation).
Case 3
Age 30, Primip, Black African-Caribbean ethnicity, who was diagnosed aged 22 with mitochondrial genetic mutation (m.3243A4 > G) following onset of blackouts and diabetes. Initially she had planned for pre-implantation genetic diagnosis but conceived spontaneously: she continues on her basal bolus regime during pregnancy. Chorionic villus sampling at 11 + 4 weeks detected 43% mitochondrial variant. Plans are in place for neonatal cardiac evaluation. Pregnancy may be challenging for women with diagnosed or undiagnosed monogenic diabetes. Our case series illustrates that monogenic diabetes can present in all ethnicities and that close oversight of glycaemic control and fetal monitoring are imperative. Additional maternal concerns about inheritance in offspring should be addressed with appropriate counselling.

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VLCKD: a suitable nutritional approach for subjects with obesity and glucose derangements?

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Introduction
The VLCKD is an established diet regimen with positive metabolic effects. Based on that, it was hypothesized that VLCKD could also have positive effects on glucose metabolism and insulin resistance, as well as obesity. Specifically, we aimed to investigate the efficacy of VLCKD on glucose metabolism in subjects with obesity compared to Mediterranean Diet.
Methods
In this cross-sectional study anthropometric parameters (weight, height and waist circumference), body composition (by bioimpedance analysis) and biochemistry data (fasting blood glucose, insulin and HbA1c) of subjects with obesity that underwent to VLCKD were collected before and at the end of active phase of the ketogenic protocol. Finally, Homeostasis Model Assessment of Insulin Resistance (HoMA-IR) was calculated.
Results
Fifty subjects with obesity were enrolled of whom 32 reached the end of the active phase of VLCKD (M5/F27, aged 37.33 ± 15.91 years). At the end of the active phase, the average weight loss was nearly 11.8% of initial weight, with significant reduction in BMI (36.90 ± 5.15 kg/m^2 vs 32.53 ± 7.54 kg/m^2, $P=0.001$), waist circumference (106.83 ± 15.8 cm vs 97.05 ± 23.36 cm, $P=0.009$) and fat mass (40.32 ± 6.01% vs 35.15 ± 11.47%, $P=0.008$). No significant changes were found in fat free mass (59.68 ± 6.01% vs 58.28 ± 16.94%, $P=0.641$). We also detected a significant improvement in fasting blood glucose (89.94 ± 11.5 mg/dl vs 82.66 ± 9.4 mg/dl, $P=0.002$) compared to the baseline. Finally, comparison from baseline to the end of active phase of VLCKD of HOMA-IR showed an improving trend in insulin sensitivity although it was not statistically significant ($P=0.127$).
Conclusion
Our results suggest that VLCKD can be a suitable nutritional approach for subjects with obesity and glucose derangements. Indeed, VLCKD allows a faster weight loss compared to other nutritional approaches[1] thus rapidly shortening the history of obesity and thus the obesity-related damage on glucose metabolism.

Finally, the same entity of weight loss is accompanied by a greater improvement of glucose metabolism when it is obtained by VLCKD compared to other nutritional approach such as MD[2-5] and this could be due to VLCKD property to preserve muscle mass, i.e. tissue important for metabolic activities.

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EP331

Mauriac syndrome: A rare complication of type 1 diabetes mellitus

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Introduction
Mauriac syndrome (MS) is a rare complication of type 1 diabetes mellitus (DM1), characterized by hepatomegaly (hepatic glycogenosis), puberty and growth delay, transaminase elevation and reduction of IGF1 (insulin-like growth factor 1). MS is more common in children and adolescents with poor glycemic control.
Case Report
A 17-years-old Type 1 diabetic boy was admitted for evaluation of growth retardation. He was diagnosed to have T1DM 15 years back. The patient maintained poor glycemic control since childhood, presenting an elevated glycated hemoglobin rate persistently higher than 10% and recurrent episodes of ketosis. Examination showed that height was 131 cm (less than 3rd percentile), weight 28 kg (less than 3rd percentile) and body mass index of 16.3. Tanner stage was G2P1. He had abdominal distension with hepatomegaly. Investigations showed HbA1c 15.2% and IGF-1 65.7 ng/ml. Liver function test showed AST 514 IU/l, ALT 277 IU/l and total bilirubin 3 mg/l. His renal function was normal. Viral hepatitis serologies and autoimmune study were negative. Ultrasound abdomen revealed hepatomegaly with a liver span of 15 cm. A liver biopsy revealed numerous hepatocytes with glycogenated nuclei, abundant cytoplasmic and nuclear glycogen deposits, and moderate portal fibrosis. Based on the clinical history and investigations, the final diagnosis of Mauriac syndrome was made. A stronger multidisciplinary approach (involving endocrinology, nutrition and psychology) was attempted in order to improve glycemic control. He was followed-up for 2 months. He had shown a reduction in hepatomegaly, a normalization of transaminase concentrations with a decrease of HbA1c concentration (from 15.2% to 11%).
Discussion
In poorly controlled DM1 patients, the hyperglycemic periods lead to accumulation of glycogen in the hepatocytes causing hepatomegaly and liver enzyme elevation. It is imperative to exclude other causes of hepatomegaly and elevated transaminase levels, including autoimmune hepatitis, viral hepatitis, hemochromatosis, and Wilson disease. The pathogenesis of growth retardation is not clear but is thought to be multifactorial. Growth failure, delayed puberty and hepatomegaly in Mauriac's syndrome improves with glycemic control.
Conclusion
Although Mauriac syndrome is rare, it should be still considered in Type 1 diabetic children with growth impairment and liver disease. Optimal glycaemic control may play an important role in preventing such an occurrence.

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Acute complications in incarcerated diabetics treated seen in the emergency room

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Introduction
The management of a diabetic patient in a prison environment is often delicate, which explains the frequency of acute complications in diabetics during the period of incarceration.
Purpose of the study
Describe acute complications in incarcerated diabetic patients and to describe their management within the endocrinology and metabolic diseases department at the CHU IBN ROCHD in Casablanca.
Method
This is a retrospective descriptive study over a period of 2 years from January 1, 2020 to November 30, 2022, including diabetic patients who consulted for acute complications in the endocrinology department during their period of incarceration.
Results
During this study period, 86 detained diabetics consulted for acute complications. Among them, 6 were female (7%), against 80 male patients (93%). The average age of prisoners was 36, with an age range of 18 to 68. Among the population studied, 83.5% had at least one toxic history (tobacco, alcohol, cannabis and psychotropic drugs), most of the patients, i.e. 78.6%, were type 2 diabetics and 21.4% type 1 diabetics with an average duration of diabetes of 15.4 years, 63% of patients were on insulin therapy while 27.4% were on oral antidiabetics and 9.6% on no treatment. The most common reasons for consultation were diabetic ketosis in 54.6% of cases and major hyperglycemia in 42.3% of cases. Among the causes of decompensation, there was a predominance of respiratory infections (41.6%), urinary infections (28.4%) and diabetic foot (15.3%), discontinuation of treatment in particular insulin therapy in type 1 diabetics was involved in 12.4% of cases. Patient care required either hospitalization for a few days (on average 7 days) in 56.3% of cases, or day hospitalization in 31.5% of cases, while 12.2% of patients required only outpatient care. All patients benefited from therapeutic and nutritional education during the hospitalization period, with follow-up consultation thereafter.
Conclusion
Our study showed the high frequency of diabetes-related complications in people in prison. The development of specialized consultations, in particular by telemedicine, as well as therapeutic education are essential to improve the care of incarcerated diabetic patients.

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Sleep quality and glycemic control in type 2 diabetes

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Introduction
Sleep is essential for the proper functioning and the well-being of the body. Poor sleep quality has many negative effects on the patient health. The aim of our study was to determine the prevalence of sleep disorders in patients with type 2 diabetes and to identify the associated factors.
Methods
It is a cross-sectional study including 51 patients and conducted in the nutrition department A of the institute of nutrition of Tunis. The patients were enrolled in April 2022.Sleep quality were evaluated by Pittsburgh sleep quality index (PSQI). Poor sleep quality was defined by a score ≥ 5.
Results
The mean age of the patients was 59.1 ± 9.51 years. The mean body mass index (BMI) was 27.83 ± 5.5 kg/m^2 and the mean duration of diabetes was 12.2 ± 10.31 years. The mean PSQI score was 7.4 ± 4.03. Poor sleep quality was reported in 72.5% of cases. More than the half of these patients were women (52.9%). Only fasting plasma glucose (FPG) was significantly associated with poor sleep quality ($P = 0.001$) with a positive correlation between FPG and PSQI score; an increase of 1 g/l caused a 2 points increase of the score. Age, sex, medical history, BMI, duration of diabetes and type of antidiabetic treatment were not associated with poor sleep quality.
Conclusion
Uncontrolled diabetes is a risk factor for sleep disorders. Similarly, poor sleep quality negatively affects diabetes control. Rigorous management is needed to break this vicious circle.

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EP334

Unwanted pregnancy in diabetic women

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Introduction
Pregnancy in diabetic women is a high-risk pregnancy whose prognosis is linked to the degree of glycemic control from conception to delivery, however, a diabetic

patient is encouraged to plan her pregnancy. However, many diabetic women find themselves in a situation of unwanted pregnancy and poorly manage their diabetes during pregnancy.
Goals
Study the causes of unwanted pregnancies and their impact on the evolution of diabetic pregnancy.
Materials and Methods
A retrospective descriptive study from January 2016 to December 2022, was conducted in the endocrinology and diabetology department of the IBN ROCHD University Hospital Center in all patients followed for diabetic pregnancy.
Results
Our study included 712 patients followed for diabetic pregnancy, of which 16% of pregnancies were unwanted. In the group of unwanted pregnancies: The most dominant age group was between 25-35 years old with an average age of 32 years, of which 70% were of low socioeconomic level and 55% were multiparous. A glycemic imbalance was objectified in 40% of parturients with an average HbA1C of 9%. The contraceptive methods most used were: 39% of estrogen-progestogens in which 72% of the causes of pregnancy were forgetting to take the pill, 27% were the cessation of contraception by a health professional because of diabetes, 7% under the intrauterine device with poor monitoring, 4% under microprogestogens; and 11% under male condom or withdrawal; while 39% were not under any contraceptive method. Among the parturients, 42% were difficult to balance. The evolution of pregnancy was complicated by preeclampsia in 15% of parturients and macrosomia in 20% of newborns.
Conclusion
Pregnancy in diabetic women requires close glycemic monitoring to ensure perfect glycemic control. Contraception in Morocco is available at the health center, while its use by parturients is still unknown, which leads patients to unwanted pregnancies. Hence the need to educate patients and health professionals on the benefits of effective contraception and good glycemic control in preconception.

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Impact of ramadan on the course of diabetic pregnancy

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Introduction
Pregnancy is a state of increased insulin resistance and insulin secretion and reduced hepatic extraction of insulin; thus fasting during pregnancy seems to cause a high risk of morbidity and mortality for the fetus and its mother. This group of diabetic patients is exempt from fasting.However, for young patients or not, Ramadan is accompanied by a change in lifestyle in particular a change in eating habits as well as a disruption of the sleep cycle and a decrease in physical activity, directly influencing the glycemic balance during this holy month.
Objective
To assess the impact of lifestyle changes during the month of Ramadan on glycemic control by assessing dietary habits, sleep quality, and physical activity during this month.
Patients and Methods
Prospective cohort study conducted at the Endocrinology-Diabetology Department of the CHU Ibn Rochd – Casablanca, in patients hospitalized or followed in consultation for diabetic pregnancy; carried out during the month of Ramadan 2022.
Results
Our study included 41 patients, of whom 66% had gestational diabetes, 10% were type 1 diabetics, and 24% had type 2 diabetes. The average age of the participants was 30 years and the average age of their pregnancy was 28 weeks. at the time of carrying out the study. 5 patients (12%) decided to fast and the median number of fasting days was 21 days. The total daily caloric intake before the month of Ramadan was 2302 Kcal with an average carbohydrate intake of 41%, 25% lipids, and 20% protein. While during the month of Ramadan, the average caloric intake was 2503 Kcal/d, with an average intake of carbohydrates of 49%, lipids of 32%, and proteins of 14%. Moderate physical activity was practiced in 30% of patients, while 63% of patients were sedentary. Weight gain was noted in 70% of our parturients with an average of 3 kg in 1 month. Sleep quality was impaired in 70% of patients, as was sleep quantity in 90% of parturients with less than 7 hours of continuous sleep.
Conclusion
The Ramadan period has an effect on the diet with an increase in the consumption of fast sugars and lipids as well as a reduction in physical activity and an alteration in the quality and quantity of sleep.

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Predictive factors of in-hospital duration of stay in diabetic patients in a medical unit at a university hospital

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Background
Patients with diabetes mellitus (DM) have been reported to have longer duration of in-hospital stay (DS). Identifying factors influencing their DS may help in the decision-making process especially in a public health setting.
Aim
We aim to compare DS in patients with and without DM admitted to a medical unit in a university hospital and to determine the predictive factors of DS in patients with DM.
Methods
A cross sectional study was conducted over a 6 months period from March to September 2020. It included patients admitted to the Medicine department at Tahar Sfar university hospital in Mahdia, Tunisia over that period.
Results
One hundred and Fifty patients were admitted during the study, 106 of which (70.6%) were patients with DM. Median DS was 7 [5-10] days, and was shorter in presence of DM (7 [5-8] days vs 10 [6-14] days, $P=0.002$). In diabetic patients, DS was not correlated to age ($P=0.339$) and there was no significant difference in LS according to gender ($P=0.659$). DS was not correlated to weight, Body Mass Index (BMI), or temperature upon admission. DS was longer in patients presenting with concomitant infection (7.5 [6-10.25] vs 7 [5-8] days, $P=0.026$). There was no difference in DS in patients with Type 1 DM and Type2 DM ($P=0.89$). The presence of complication of DM did not impact the DS ($P=0.47$). DS was positively correlated to White blood cells count ($P=0.048$, $r'=0.19$), Neutrophil ($P=0.014$, $r'=0.24$), PTH ($P=0.002$, $r'=0.31$), initial CRP ($P<10\text{-}4$, $r'=0.37$) and early morning cortisol ($P=0.036$, $r'=0.2$) levels. It was also negatively correlated to hemoglobin ($P=0.005$, $r'=-0.28$), HbA1c ($P=0.01$, $r'=-0.25$), measured plasma calcium ($P=0.049$, $r'=-0.21$) and albumin levels ($P=0.02$, $r'=-0.32$).
Conclusion
In our study DS was shorter in diabetic patients. These findings are opposed to previous data (1). In diabetic patients, the presence of infection and elevated inflammatory markers was positively associated to DS, while biological markers of malnutrition were negatively correlated to DS. These results suggest that such biomarkers can be used as part of an individualized decision making when admitting patients with DM.
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Issues of diabetes management in resource poor setting

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Issues
In developing nations diagnosis of diabetes brings mental-trauma/depression in family. Focused treatment for pediatric age-group is unavailable in developing-countries. 26% of diagnosed diabetics are children's. Adequately trained physicians/Nurses in issues of pediatric-diabetes provide continuity of care, relief from depression and smooth transition from diagnosis to treatment. Qualitative collaborative relationship between these makes diabetics life bearable. Our NGO-project highlights significance of relationship between nurses and diabetic-children in community clinic setup of rural India. For Diabetes, it's assumed that depression is inevitable sequel to diagnosis. Retrospective analysis of past studies shows—counselling improves QOL & attitude towards diabetes-treatment.
Aims
To describe care issues in diabetic-children's. Observe/modify nature of relationship between nurse and child. To evolve comprehensive treatment plan for patients and families.

Methods
A retrospective analysis of data base from 7 rural health-clinics. Specialized therapy/support to pediatric-age-group not available at any centre. Total 117 children's [4-13 years] diagnosed with diabetes. 23 had additional endocrine/-metabolic problems. Nursing/medical care plan analyzed. No specialized trained personal in rural/tribal India. Opinion/needs from patients' families collected on feedback questionnaire. Then we trained 10 nurses & 2 physicians for handling pediatric cases [4 weeks training].
Results
Out of 117, 41 discontinued Rx due to improper counseling/guidance. 3 died. Patient/family's feedback highlights: Better access to newer drugs-delivery-systems, psychosocial support, follow-up-plan. Nurses/physician be sensitized in pediatric care-issues. Main issues of concern were: illness and coping with their feelings. Initial impact of diagnosis and a search for solution? Expectations for future life & its quality? Concerns of cost of RX Availability of proper follow-up centers in rural areas of developing nations.
Conclusion
Multifaceted Relationship between physician/nurse and Diabetics children's is crucial. Follow-up must be given priority. This relationship provides better continuity of treatment. We show concerns/difficulties while working in Asian set-up for paediatric diabetis to international experts/seniors at ece.

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Residual metabolic effect after cessation of liraglutide therapy in patients with type 2 diabetes

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Objective
The aim of our study was to evaluate the possibility of maintaining the metabolic effects of liraglutide 3.0 mg treatment after it's cessation.
Methods
The study included 8 patients with type 2 diabetes (T2D) and obesity who received liraglutide 3.0 mg daily for 9 months. All of them successfully reduced body weight, insulin resistance level (IR), volume of visceral adipose tissue, HbA1c level. After discontinuation of liraglutide in 2019, these patients did not use GLP-1 analog therapy for 3 years. After 3 years patients were assessed for the following: weight, BMI, glucose, insulin, HbA1c, body composition, hyper-insulinemic euglycemic clamp test with M-index evaluation. Results were compared with similar data collected in 2019 before the start of GLP-1 analog therapy (0-month point), 9 months after the start (9-month point), 3 years after cessation (45-month point).
Findings
BMI did not significantly change between 9-month and 45-month points, though the amount of total and visceral fat increased. Cessation of liraglutide 3.0 mg caused HbA1c deterioration, but according to M-index insulin resistance decreased (Table 1). When comparing data at 0-month and 45-month point we still saw the improvement in fasting glycemia and the non-significant reduction of HbA1c (Table 2).

Table 1 Comparison of data collected on 9-month point and 45-month point

Indicators		**Me (Q1;Q3)**	***P***
	9 month	45 month	
BMI	37.96 (32.9;40.2)	38.75 (38;43)	0.093
M-index	1.09 (0.96;2.6)	2.58 (1.26;3.5)	**0.036**
Fasting glucose	6.08 (5.1;6.7)	7 (5.7;8.8)	0.093
Fasting insulin	22.7 (14.3;30)	12.2 (7.3;17.1)	**0.012**
HbA1c	6 (5.5;6.4)	7.1 (5.95;8.6)	**0.025**
Total fat (%)	37.5 (33;41)	48.6 (40.4;52)	**0.012**
Visceral adipose tissue (volume)	170 (127.5;212.5)	255.65 (200;287)	**0.012**

Table 2 Comparison of data collected on 0-month point and 45-month point

Indicators		**Me (Q1;Q3)**	***P***
	0 month	45 month	
BMI	42.52 (38.5;43.5)	38.75 (38;43)	0.207578
M-index	1.295 (0.9;2.2)	2.58 (1.26;3.5)	**0.035692**
Fasting glucose	9.78 (6.4;11.47)	7 (5.7;8.8)	**0.01729**
Fasting insulin	18.98 (13.4;30)	12.2 (7.3;17.1)	**0.011719**
HbA1c	7.95 (7.1;8.6)	7.1 (5.95;8.6)	0.233356
Total fat (%)	39.6 (38.5;42.8)	48.6 (40.4;52)	0.05
Visceral adipose tissue (volume)	215 (142.5;255)	255.65 (200;287)	0.161429

Interpretation
Liraglutide 3.0 mg therapy may possibly have significant long-lasting metabolic effects even after its cessation. Funding: RSF grant 22-15-00365.

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Efficacy of Dapagliflozin in patients with Non-alcoholic Fatty Liver Disease: A Single Center Experience

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Aim
Non-alcoholic fatty liver disease (NAFLD) is a common comorbidity with type 2 diabetes and a few agents such as pioglitazone and metformine has been shown to beneficial effects. SGLT-2 inhibitors are used in the treatment in type 2 diabetes (T2D). It has been shown that they can the effectivenes of improve liver function in patients with NAFLD as well as in T2D. In our study we aim to elucidate the effectiveness of SGLT-2 inhibitors as second line treatment for NAFLD patients with T2D by comparing with pioglitazone.
Patients and measurements
NAFLD patients with T2D ($n=34$) who did not use SGLT2 inhibitors (dapagliflozin, empagliflozin) or pioglitazone were enrolled in the current study. Patients were divided into 3 subgroup who were treated with Dapagliflozin 10 mg, empagliflozin 10 mg and pioglitazone 45 mg as a second line treatment of T2D. Before and after the treatment; all biochemical parameters of the patients' were screened as well as the body mass index and waist circumference. Patients were also followed-up the same treatment during the 16 weeks. Screening for NAFLD was performed using MRI-based (3.0 T, Ingenia, Philips Medical Systems, Best, The Netherlands) proton density fat fraction before and after the treatment. All patients were matched in case of baseline body mass index (BMI), gender differences.
Results
At the end of the 16 weeks after the treatment HbA1c levels (%) of the patients treated with Dapagliflozin ($P=0.04$) and Empagliflozin ($P=0.01$) were decreased compared to baseline levels but not pioglitazone ($P=0.108$). While changing of waist circumference of the patients treated with dapagliflozin ($P=0.001$) or empagliflozine ($P=0.008$) were statistically significant, patients with pioglitazone were not significant ($P=0.801$). Baseline hepatic steatosis measurements of the patients' treated with Dapa, Empa and Pio were 0.19 ± 0.09, 0.17 ± 0.07 and 0.14 ± 0.09, respectively. At the end of the study; measurements of patients' were 0.11 ± 0.09 ($P=0.001$), 0.13 ± 0.08 ($P=0.09$) and 0.12 ± 0.14 ($P=0.360$), respectively.
Conclusion
Dapagliflozin may have a beneficial modulatory effect on NAFLD as well as the T2D.

Table 1 Change in baseline and study completion for three group

Group	Dapagliflozin	Empagliflozin	Pioglitazon	Total
Body mass index (kg/m^2)				
Baseline	33.471	33.915	33.826	33.340
Study completion	31.7512	32.5099	34.4236	
P	0.001	0.006	0.493	
Glycosylated haemoglobin (%) mean				
Baseline	7	7.45	7.65	7.3
Study completion	6.53	6.91	6.39	
P	0.046	0.019	0.108	
Amount of Fatty Liver in MRI (%)				
Baseline	19.4	17.3	14.9	17.7
Study completion	11.2	13.9	12	12.4
P	0.001	0.92	0.36	0.000

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EP340

Factors associated with poor diabetes control in insulin-requiring elderly subjects

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Introduction
Management of diabetes in older adults is complicated by the many comorbidities that may interfere with the use of certain oral antidiabetic agents, and the associated geriatric syndromes, psychiatric disorders, and high risk of dependence in this age group. The objective of our study was to determine the factors associated with poor diabetes control in insulin-requiring elderly subjects.
Methods
A cross-sectional study on type 2 diabetic insulin dependent elderly recruited from the outpatient endocrinology consultation over a period of 2 months from June 2021 to July 2021.
Results
We recruited 100 patients with a mean age of 70.8 ± 5.8 years and a sex ratio of 0.85. The mean durations of diabetes and insulin therapy were 15.67 ± 6.7 years and 7.69 ± 6 years, respectively. The mean level of HbA1C was 9.85 ± 1.7%. The majority of patients had uncontrolled diabetes (90%). Poor diabetes control was associated with low socioeconomic level (77.8% vs 30%; $P=0.001$), uncontrolled high blood pressure (54.4% vs 20%; $P=0.039$), not removing insulin from refrigerator at least 30 minutes before use (82.2% vs 50%; $P=0.018$), not checking expiry dates of insulin and needles (75.6% vs 40%; $P=0.018$), using long needles (72.2% vs 30%; $P=0.007$), no hand washing before injection (34.4% vs 0%; $P=0.025$), no disinfecting the rubber of the insulin vial or pen cartridge (92.2% vs 70%; $P=0.026$), the incorrect re-suspension technique for cloudy insulin (no rolling or tipping the vial or cartridge of cloudy insulin: 91.1% vs 50%; $P<10^{-3}$ and 92.2% vs 60%; $P=0.02$, respectively), no rotating of the injection site (36.7% vs 0%; $P=0.019$), skiping the injections (51.7% vs 10%; $P=0.012$), bleeding or hematoma at the injection site (57.8% vs 20%; $P=0.023$) and the loss of insulin from the injection site (44.9% vs 10%; $P=0.033$). After multivariate analysis, no rolling and no tipping the vial or cartridge of cloudy insulin were factors independently associated with poor diabetes control (OR = 12.599; 95% CI, 2.5 to 63.35; $P=0.002$ and OR = 10.188; 95% CI, 1.825 to 56.875; $P=0.008$, respectively).
Conclusion
The challenge to overcome in optimizing diabetes management is not a lack of recommendations or scales. However, it is their adoption and implementation by caregivers and patients that dismisses the need for optimal insulin injection technique as a fundamental driver of diabetes control that could turn the game around.
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EP341

Metformin-Associated Lactic Acidosis: A Case Report
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Introduction
Metformin is widely used as the first-line therapy for patients with type 2 diabetes, and its most common adverse effects are gastrointestinal. Metformin-associated lactic acidosis (MALA) is a rare but serious adverse effect in patients with type 2 diabetes or patients who attempt suicide with metformin overdose. Here, we report the case of a 22-year-old woman who developed severe lactic acidosis after high-dose metformin was taken for a suicide attempt.
Case
A 22-year-old woman with anxiety disorder and depression developed life-threatening lactic acidosis after taking high doses of metformin to attempt suicide. The patient received approximately 30 g of metformin. She applied to the emergency department with slurred speech and nausea. In her initial laboratory findings, arterial blood gas pH was 7.41, bicarbonate 14 mmol/l, anion gap 13 mmol/l, lactate 7.5 mmol/l, and creatinine of 1.44 mg/dl. Then she deteriorated and arterial blood gas pH became 6.96, bicarbonate 5.8 mmol/l, anion gap 33 mmol/l, lactate 23.9 mmol/l, and creatinine of 1.99 mg/dl. Renal replacement therapy was initiated. After one dialysis session, her severe acidemia resolved over time. She was discharged from the hospital without any complications. A Naranjo assessment score of 9 was obtained, indicating a probable relationship between the patient's lactic acidosis and her use of the suspect drug.
Conclusion
MALA is a well-known and life-threatening complication of metformin. Vomiting and diarrhea are the first signs of MALA. Even if severe lactic acidosis may not be apparent at first as in our case clinicians should be aware that lactic acidosis may develop. Severe lactic acidosis can be treated with renal replacement therapy because metformin is dialysable.
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EP342

Case report: Association of Fenugrec and curcuma as a cause of hypoglycémia
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Introduction
Research in the past two decades has shown that Fenugrec seeds help to lower blood glucose in patients with diabetes. Its role as an antidiabetic, by reducing fasting blood glucose levels and improved glucose tolerance in human subjects was reported Curcuminoids have been shown to improve insulin resistance, decrease glucose and insulin levels, increase adiponectin release, and reduce the levels of leptin, resistin, interleukin (IL)-6 IL-1b, and tumor necrosis factor-a in patients with type 2 diabetes.
Case Report
A 48 years old patient that have background type 2 of diabete for 19 years and hypertension for 4 years. She is taking fenugrec and curcuma for 3 months, making a periodic hypoglycemia of variable hours estimated 0.30 g/l felt by tremor and sweat, yielding by dates or honey by itself. It should be noted that these hypoglycemia are noticed one week after taking the fenugrec and curcuma and combination and the patient does not report of meal skipping or intense physical activity which may be the cause of the hypoglycemia. Examination revelated normal vital parameters slate stain or melanoderma. Hormonal profile revealed cortisolemie = 16ug/dl. We linked this hypoglycemia to taking the fenugrec and curcuma combination, so the decision was to stop taking these plants and monitor the patient glycemic cycle. The glycemic cycle brought back one week after his hospitalization did not show hypoglycemia.
Discussion
Scientists have demonstrated that the amino acid 4 OH Ile in fenugreek seeds increases glucose induced insulin release in vitro in human and rat pancreatic islet cells, while others showed that fenugreek seed extract phosphorylates a number of proteins, including the insulin receptor, insulin receptor substrate 1 and p85 subunit of PI3 K, in both 3T3 L1 adipocytes and human hepatoma cells, HepG2.The dose of fenugreek seeds given also affect the blood sugar levels and higher dosages do show more hypoglycemic effect as shown in the previous trials. The dose range was wide ranging from 2 to 25 g/day. The studies showed that the use of Curcuma longa or curcumin (in different formulations) showed significant reduction of lipid peroxidation, fasting blood glucose levels, Glycated hemoglobin (HbA1C), triglycerides, total cholesterol, LDL-c, C-Reactive Protein, systolic and diastolic blood pressure.
Conclusion
Curcumin and funugrec are a natural anti-inflammatory and anti-diabetic agent representing a safe and low-cost alternative for this condition's therapeutic approach, although it is still necessary to know its effective dose to avoid hypoglycemia.
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EP343

The effect of quadriple combination therapy including SGLT-2 inhibitor in type 2 diabetes
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Introduction
Before launching of SGL¬T-2 inhibitor, triple combination of TZD with metformin and DPP¬4 inhibitor was best option for delaying progression of diabetes by improving insulin resistance and secretory dysfunction. SGLT-2

inhibitor can be used as first combination therapy with metformin, but add on to any diabetic combination will be favorable in terms of body weight and cardiovascular risk reduction, especially in long duration of diabetes with relatively high risk of cardiovascular complication. SGLT-2 inhibitor is better than sulfonylurea in preserving beta cell reserve and preventing diabetic complication, so we tried to know the effect of SGLT-2 inhibitor add on to triple combination because there are few studies about those combination therapy excluding sulfonylurea.
Subject and Methods
In 62 patients with relatively long duration of diabetes that did not reach the goal of HbA1c 7.0% with triple combination with metformin, DPP-4 inhibitor and TZD, SGLT-2 inhibitor-10 mg of empagliflozin or usual or half dose dapagliflozin(5mg) was added due to economical cause because add on to TZD or DPP-4 inhibitor is not covered by national insurance in this country. The clinical characteristics and changes of HbA1c by dose of SGLT-2 inhibitor, body weight were assessed.
Results
The mean age was 63.5±9.2 and duration of diabetes was 13.6±6.2 years. The fasting C-peptide was 2.26±1.09 ng/ml and BMI was 27.3±3.7. The mean of 3 months and just before add on HbA1c level was 7.89±1.00%. The HbA1c level was 7.24±0.87% and 7.14±0.71 after 6 and 12 months after add on, so it was lowered by 0.65% and 0.76% each. HbA1c lowering effect was greater in usual dose of dapagliflozin than half dose and 10 mg of empagliflozin (0.86% vs 0.49% and 0.57% at 6 months, 1.12% vs 0.41 and 0.75% at 12 months, $P<0.05$). Body weight was decreased by 1.89±2.82 after 6 months.
Conclusion
SGLT-2 inhibitor including half dose of empagliflozin and dapagliflozin add on to triple combination of TZD with metformin and DPP–4 inhibitor was effective in body weight as well as glucose lowering effect, so quadriple combination therapy except sulfonylurea can be effective in glucose control and preserving beta cell function before initiation of insulin treatment.

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EP344

Impact of "Taraweeh" prayer on glycemic control in diabetic patients during ramadan

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Introduction
During Ramadan, diabetic patients should be encouraged to maintain normal physical activity. The physical efforts involved in the "Taraweeh" prayers, are considered part of their daily physical activity. Patients are more likely to reach their HbA1c targets and reduce weight when night prayers are performed.
Objectives
The objective of our study was to assess the impact of the "Taraweeh" prayer on glycemic control and weight change, to assess the risk of hypoglycaemia linked to these prayers, and thus to assess the possibility of encluding these prayers into the diabetes care during Ramadan.
Materials and Methods
Prospective case-control study conducted at the Endocrinology-Diabetology Department of the UHC Ibn Rochd – Casablanca, in type 2 diabetic patients. The study group included 100 subjects practicing the "Taraweeh" prayers, and the control group 100 patients not practicing them.
Results
The average age of our patients was 54 years (38-69 years). In pre-Ramadan the average HbA1c was 8.7%, and the average weight 87.4 kg. Among our patients, 83.7% did not practice any physical activity before Ramadan, and 62.5% were fasting. According to the days of prayers performed, the patients in the study group were divided into 3 groups: <10 days (8.4%), 10-20 days (76.6%), $>$ 20 days (15%). Among our participants, 89% walked an average of 5 min to the mosque. On destiny's night, prayers were performed by 86.2% of the patients, with an average of 20 "rakaa". In comparison with the control group, a reduction in HbA1c of 1.8% (0.7-2.3) on average was observed in our patients ($P<0.001$), with an average weight loss of 5.6 kg ($P<0.001$). This is proportional to the number of days of prayers performed, and all the more so in fasting patients. Hypoglycemia was concomitant with prayers in 27.8% of our patients, with a preponderance in patients on insulin or on sulfonylureas, and in particular on destiny's night.
Conclusion
The "Taraweeh" prayers must be included into the daily physical activity of our diabetic patients, allowing them to achieve a better glycemic balance, as well as weight loss at the end of the holy month. Hence the interest of motivating them to this practice during the pre-Ramadan consultation, with caution to avoid hypoglycaemia.

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EP345

Factors Contributing to Noncompliance With Diabetic Medications in Patients With Type 2 Diabetes Mellitus in India

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Background
Type 2 diabetes mellitus (T2DM) is a chronic medical condition characterised by persistently high blood glucose levels. T2DM risk factors include obesity or being overweight, a high BMI, genetics, and certain medical conditions. Medicine adherence is very important for the management of T2DM and if it is not well controlled by lifestyle modification or DM regulatory medications, it can lead to complications. The goal of this study is to identify the factors that contribute to noncompliance with oral diabetes medications in T2DM patients in India.
Methodology
A cross-sectional questionnaire study was conducted on T2DM patients in Central India via a link distributed on social media, and the contributory factors of diabetes medication noncompliance were assessed.
Results
The study included 324 participants in total. In terms of medication adherence, 199 (61.4%) participants were mostly adherent to their medications, 97 (29.93%) were not, and 28 (8.6%) were occasionally adherent. According to participants, the most commonly reported factors contributing to noncompliance with DM medications were forgetfulness, a lack of knowledge about the importance of diabetes control, and medication side effects. Age, marital status, occupation, comorbidities, diagnosis period, and previous complaints of DM complications all had significant associations with DM medication adherence.
Conclusion
The study's findings revealed that adherence to DM medications was suboptimal among T2DM patients in Central India. Several factors were discovered to have an effect on medication adherence in this study. More research is needed to include other factors that may influence adherence, such as patient-provider communication.

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EP346

Lifestyle in a group of adolescents with type 1 diabetes

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Introduction
Type 1 diabetes (T1DM) is an autoimmune disease that requires insulin treatment from the time of diagnosis. The evidence about the influence of lifestyle on the course of T1DM is increasing. The aims of our study were to evaluate the lifestyle of a group of boys with type 1 diabetes and to study their glycemic control.Method: This is a descriptive cross-sectional study conducted at the National Institute of Nutrition in Tunis.The level of physical activity (PA) was evaluated using the International Physical Activity Questionnaire (IPAQ). A nutritional survey was done for each patient using the 24-hour recall method. A high-carbohydrate diet was defined as a carbohydrate intake greater than 5 g/Kg of ideal weight/Day.The ideal weight was determined by the CREFF formula. We analyzed the CGM data for each patient and we calculated the coefficient of variability of glucose (CV), mean of glycemic excursions (MAGE) and the mean of daily differences (MODD).

Results
We included 37 boys with type 1 diabetes in our study, with an average age of 17 ± 2 years old. The mean duration of diabetes was 6 ± 4 years. The average body mass index was 19.5 ± 2 kg/m^2; two patients in the study population were overweight. Among our patients, 13.5% had a high level of PA, 48.6% had a medium level and 37.8% had a low level PA. The average total caloric intake was 2432 ± 665 Kcal/d, distributed as follows:2676 ± 300 Kcal/d for patients with high PA, 2440 ± 800 Kcal/d for patients with medium level of PA and 2320 ± 562 Kcal/d for patients with low level PA. The mean carbohydrate intake was 291 ± 145 g/d (46 ± 7% of the total caloric intake). However, 28.6% of patients had a high-carbohydrate diet. In addition the average protein intake was 84 ± 29 g/d (14 ± 4% of the total caloric intake)and the average fat intake was 98.5 ± 31g/d (36 ± 5% of the total caloric intake).The mean glycated hemoglobin level was 9.8 ± 1.8%, only two patients had Hb1Ac ≤7%.Time in range varied between 4 and 88% with an average of 37 ± 18%.Time below range was between 0 and 36% with an average of 6.6 ± 8%.The mean of time within range was 55.9 ± 21%.The average coefficient of variability of glucose, was 40 ± 10%, that of MAGE was 150 ± 45 mg/dl. Moreover the majority of patients (91.9%) had a MAGE > 65 mg/dl. The average MODD was 85 ± 40 mg/dl.
Conclusion
Dietary measures are difficult to apply in adolescents and this can induce poor glycemic control. Nutritional education must be regularly maintained associated to insulin therapy.

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EP347

"We must always think that there may be something else". Cushing's disease and a rare partial hereditary lipodystrophy type 6 associated with retinos pigmentosis, coexistence of both diseases in a single patient

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Lipodystrophic syndromes are a heterogeneous group of usually rare disorders, which have in common the selective and irreversible deficiency of adipose tissue in the absence of nutritional deprivation or catabolic state. Clinically, they are characterized by insulin resistance, related to a state of hypoleptinemia, with manifestations such as polycystic ovarian syndrome, type 2 diabetes mellitus, severe hypertriglyceridemia, and steatohepatitis among their most frequent metabolic complications. Within the lipodystrophic syndromes we must differentiate between congenital and acquired and within the congenital, generalized and partial. Partial congenital lipodystrophy has an asymmetric distribution of fat, with loss of adipose tissue in the extremities, predominantly in the lower limbs, thighs, and buttocks, with the consequent accumulation of fat in the neck, chin, and abdominal fat. That is why, among its differential diagnoses, we must include Cushing's syndrome in patients. We present the case of a patient, with Cushingoid phenotype, with diabetes mellitus, severe hypertriglyceridemia and visual disturbances with a diagnosis of retinitis pigmentosa, who presents data of ACTH-dependent biochemical hypercortisolism, confirmed a pituitary macroadenoma on MRI, the patient underwent resection. Transsphenoidal adenoma, confirming the presence of an ACTH-producing pituitary adenoma in the Immunohistochemistry with ACTH + receptors in the tumor. At first, it seemed strange to us to associate retinitis pigmentosa with Cushing's disease, but no reports were found. We request a genetic study of retinitis pigmentosa in our center. We are informed that two important genetic changes have been detected in other genes: A homozygous change in the LIPE gene (c.551C>A (p.S184*). This gene has been associated with autosomal inheritance type 6 partial lipodystrophy recessive. We conclude with a LIPE gene mutation associated with retinitis pigmentosa in a patient with Cushing's adenoma.

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EP348

Modified Appleby Procedure in the Treatment of Pancreatic Neoplasms

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Introduction
Pancreatic neoplasms portray the 12th most prevalent neoplasm worldwide, determining a five-year survival of only 5 to 10% including all stages. Despite tumoral aggressiveness, the modified Appleby procedure can be performed in selected patients, representing a curable alternative in borderline-resectable or locally advanced pancreatic tumors' treatment in the context of a multimodal practice. Objectives: This work aims to review the state of the art regarding the patients who may benefit from resection using the modified Appleby procedure, the pre- and post-operative procedures to increase survival, and the postoperative outcomes.
Materials and Methods
Research was conducted within the PubMed and Embase databases from July 2022 to January 2023, including single or multicenter articles relative to the modified Appleby procedure but comprising a multimodal approach to pancreatic neoplasms and not only the surgical technique, and papers concerning patients over the age of 18 years.
Results
Out of the 373 articles identified and after extracting duplicates, 267 records were accessed for a title and abstract screening. Afterward, by applying the inclusion and exclusion criteria to the remaining articles and conducting a further extensive reading of the remaining articles, 53 papers were included in this review. Secondary terms relevant to this topic were also used, allowing detection of additional research, thus totalizing the 56 publications included.
Discussion
The initial assessment of pancreatic neoplasms' resectability was appraised, as well as the modified Appleby procedure's surgical technical options, its difficulties, morbidity, and mortality. Patients were addressed based on a multimodal strategy to increase survival, therefore neoadjuvant/adjuvant chemotherapy indications and regimens were also discussed.
Conclusion
When applied to borderline resectable and locally advanced pancreatic cancer, the efficacy of the modified Appleby procedure alone is limited, but the combination with neoadjuvant chemotherapy offers the greatest chance of achieving an R0 resection. Many surgical technical options are available, with or without preoperative artery embolization, but the best results published to date were observed when employing robotic surgery with a retroperitoneal-first approach. However, the indication for performing this surgery and all its perioperative components are still a matter of debate.

Keywords: Appleby procedure, pancreatic neoplasms, celiac axis infiltration, preoperative embolization, liver infarction.
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EP349

Comorbid depression and cardiovascular disorders in patients with type 2 diabetes

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Introduction
Depression often occurs as comorbid and concomitant disorder in patients with type 2 diabetes (T2D) complicating the course and outcome of the disease, prolonging the treatment and accelerating complications of diabetes, especialy cardiovascular complications. Numerous researches show significant presence of cardiovascular disorders in depressed patients with T2D that show up several year after first depressive episode. Mortality caused by cardiovascular disorders in depressed patients with T2D is 50% higher than in general population. Comorbid depression and cardiovascular disorders in diabetic patients making worse health condition, increasing suffering, making hard treatment and outcome is not good.
Aim
The goal is to confirm presence of cardiovascular disorders in depressed patients with T2D as the most common comorbid cardiovasvular diseases.
Methods
A retrospective study has been conducted using data from medical history of 274 depressed patients with T2D hospitalized and treated at the Psychiatric Clinic, University Clinical Center of Republic of Srpska.These parameters were assessed: sex, age, number of hospitalizations, marital and employer status, comorbid disease, body mass index, presence of cardiovascular disorders and laboratory tests (glycemia, lipid status and renal function parameters). Data were presented using tables and graphs.

Results
Cardiovascular disorders in patients with T2D comorbidity with depression we found in 126 patients (45.9%), 96 of them were males and 30 females. Hypertension in comorbidity with depression in diabetic patients was diagnosed in 83 patients (65.8%), while comorbid with cardiac disordes was found in 45 patients (35.7%). In the group of depressive diabetics patients with cardiovascular disorders, 65% of them had unsatisfactory level of glycoregulation.
Conclusion
Depression is often accompained by cardiovascular disorders in patients with T2D. It is very important to recognize this comorbidity in order to treat it successfully and to make better treatment's otucome.
Keywords: diabetes mellitus type 2, depression, cardiovascular disorders.
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EP350

Hepatopathy of Mauriac síndrome: a case report
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We report the case of a 34-year-old woman with a personal history of type 1 diabetes mellitus (DM1) since she was 9 years old. Very poor chronic metabolic control stands out despite multiple insulin schemes with multiple complications: nephropathy, retinopathy and peripheral neuropathy. She was admitted to the hospitalization floor due to diabetic ketoacidosis. At admission Hba1c of 15.3%. During admission after treatment with IV insulin, improvement in glycemic control. Nine days after admission, she began with symptoms of edema in all 4 limbs, distension, and abdominal pain. On examination, she presented a height smaller than expected (150 cm), slightly overweight (59 kg) and extensive hepatomegaly. Liver function tests showed an increase in transaminases (GOT 359 IU/l, GPT 210 IU/l) and alkaline phosphatase (190 IU/l). Viral and autoimmune etiology was ruled out. An abdominal ultrasound was performed, showing a large hyperechogenic homogeneous hepatomegaly. It was decided to perform a percutaneous liver biopsy, which revealed a liver parenchyma with preserved architecture, with hepatocytes with large, clear cytoplasm, with a striking membrane and some empty nuclei with a glucogenic appearance. Cytoplasms show intense periodic acid-Schiff (PAS) staining, but PAS-diastase negativity, confirming cytoplasmic glycogen deposition. No reticulin fibrosis, inflammation, or steatosis is observed. The most probable diagnosis is hepatic glycogenesis secondary to diabetes. Six months later, after improvement in glycemic control, with an Hba1c of 6.6%, normalization of transaminase and alkaline phosphatase levels, resolution of hepatomegaly. The Pierre Mauriac syndrome described in the year 1930, is characterized by growth failure, cushingoid appearance, hepatomegaly and hypertransaminasemia, in a patient with chronic uncontrolled DM1. The most common age of presentation is usually in adolescence, although cases have been described in both children and adults. The hallmark of this syndrome is extreme liver enlargement from massive acucumulation of glycogen. The diagnosis of hepatopathy requires high clinical suspicion and the presence of glycogen accumulation must be corroborated with a liver biopsy. The accumulation of glycogen in hepatocytes is partly caused by long periods of hyperglycemia, in which glucose enters the hepatocyte independently of insulin and is converted to glycogen. Mauriac syndrome is currently a rare cause of liver disease, due to improvements in control and treatment of patients with DM1. However, some cases are described in people with complicated social situations or without therapeutic compliance. This is a reversible condition after improvement in glycemic control with adequate insulinization.
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EP351

Predictive factors of diabetic nephropathy in type 2 diabetics
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Introduction
Uncontrolled hyperglycemia in diabetes is a common cause of microvascular complications, including diabetic nephropathy (DN). Despite improvements in the management of type 2 diabetes (T2DM), diabetic nephropathy is still associated with high morbidity and mortality. The objective of our study is to evaluate the predictive factors of DN in adults with T2DM in order to prevent its development.
Patients and Methods
A retrospective study, including 300 patients diagnosed with T2DM hospitalized in the endocrinology department of Farhat Hached Hospital in Sousse between 2018 and 2019. DN was defined with a persistent albuminuria (>300 mg/dl) that is confirmed on at least 2 occasions 3-6 months apart. Predictive factors for DN were determined by univariate logistic regression analysis.
Results
It is about 272 patients with a mean age of 58 years. The sex-ratio M/F was 0.7. The mean diabetes duration was 10 ± 8 years (1-44 years). DN was observed in 44% of patients. Approximately 91% of patients who had been diagnosed with DN were aged more than 50 years old ($P<10^{-3}$). DN was more frequent (93%) after 10 years evolution of diabetes ($P<10^{-3}$). Hypertension was present in 55% of patients with DN ($P=10^{-3}$). The mean systolic and diastolic BP were 130 ± 10 mm Hg and 70 mmHg, respectively. The majority of patients with DN (76%) had LDL-C levels above recommended targets ($P<10^{-3}$). The results of our study showed that 65% of patients with DN were not on statin therapy ($P<10^{-3}$). It was found that 69% of patients with DN had simultaneous diabetic retinopathy ($P<10^{-3}$). However, only duration of T2DM ≥ 10 years, age $>$ 50 years, LDL-C levels above recommended targets, no statin therapy and concurrent RD were significant in stepwise logistic regression analysis.
Conclusion
Our study suggests that the development of DN can be prevented by early control of its modifiable predictors such as: LDL-C levels which should be within the recommended targets with statin therapy.
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EP352

The state of the kidney in patients with type 2 diabetes mellitus post-EVRP
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Aim
Determine the state of the kidneys by the concentration of blood creatinine in patients with type 2 diabetes in post-EVRP.
Materials and Methods
Patients with type 2 diabetes who underwent EVRP were included in the 1st stage of the study. 2 groups of patients: in whom CI-AKI developed in the post-procedural period (29 patients) and patients with an uncomplicated course of the post-procedural period (27 patients).
Results
In patients with type 2 diabetes in both groups, the initial creatinine concentration significantly exceeded the CG values (90.41 ± 1.85 μmol/l and 96.89 ± 1.40 μmol/l in the CI-AKI+ and CI-AKI- groups, respectively, versus 55.60 ± 2.53 μmol/l in the CG, the reliability of comparison of both groups of DM with CG was $P<0.001$). Moreover, in the CI-AKI- group, the creatinine concentration was slightly higher than in the CI-AKI+ group ($P<0.05$). On the 4th post-procedural day: the relative dynamics in the CI-AKI+ group was 65.06% vs 16.12% in the CI-AKI- group ($P<0.001$ significance of the difference in the relative dynamics between the groups). Subsequently, the creatinine concentration in both groups decreased, reaching the initial values in the CI-AKI+ group by the 10th day after EVRP, and in the CI-AKI- group, by the 6th day of observation and subsequently decreasing significantly below the initial values, which is probably due to both hydrations after EVRP, and the use of antiplatelet therapy, and lifestyle modification.
Conclusion
During the entire post-procedure period of observation in the CI-AKI- group, the blood creatinine concentration remained significantly lower than in the CI-AKI+ group ($P<0.001$ - significant intergroup difference on the 4th day).
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EP353

Microvascular and macrovascular complications prevalence, mortality rate in type 2 diabetes patients with severe insulin resistance: A case-control study

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Some patients with type 2 diabetes mellitus (T2DM) suffer from severe insulin resistance (IR). There is still a shortage of research analyzing these patients. Relation between IR and diabetes complications, risk of mortality has been poorly described in patients with T2DM.

Objective

To evaluate the prevalence of microvascular and macrovascular complications, mortality in type 2 diabetes patients with severe insulin resistance.

Methods

It was a case control study. If T2DM patients received high insulin doses (>1 IU/kg/day) and their HbA1c $\geq 9\%$, they were assigned to the case group ($n=58$). Patients with lower insulin requirements (<1 IU/kg/day) and HbA1c $< 8\%$ were assigned to the control group ($n=62$). Participants of control group were matched by gender and BMI with the case group. Additionally, the insulin resistance was assessed according to validated eGDR (*estimated glucose disposal rate*) and HOMA-IR (*Homeostatic Model Assessment for Insulin Resistance*) mathematical formulae. HOMA-IR ≥ 2.5 indicates IR. eGDR <4 mg/kg/min reffer severe IR. Data was analyzed using SPSS 27.0 software. The level of statistical significance was set as $P<0.05$.

Results

Total of 120 participants were included, data are shown in Table 1.

Conclusions

1. Subjects with severe insulin resistance had higher daily insulin requirement, HOMA-IR value and lower eGDR.
2. The prevalence of microvascular and macrovascular complications, overall mortality in the groups was similar.
3. Diabetic neuropathy tended to be higher in the Case group.

Table 1 Baseline participant characteristics, distribution of micro- and macrovascular complications and mortality rate in the groups

Variable	Control group($n=62$)	Case group($n=58$)	*P* value
Sex, male, (*n* (%)	25 (40.3%)	28 (48.3%)	0.381
Age (years), m±SD	67.85±8.50	61.26±9.47	<0.001
HbA1c (%), m±SD	6.89±0.82	10.36±1.11	<0.001
INS/kg/d, m±SD	0.64±0.21	1.45±0.33	<0.001
HOMA-IR, median [min-max]	5.4 [3.75 - 10.05]	11.2 [6.95 - 48.41]	0.003
eGDR, m±SD	4.29±1.68	1.65±1.28	<0.001
Microvascular complications:			
Diabetic neuropathy, *n* (%)	53 (85.5%)	56 (96.6%)	0.055
Diabetic nephropathy, *n* (%)	15 (24.2%)	15 (25.9%)	0.833
Diabetic retinopathy, *n* (%)	29 (52.7%)	32 (47.3%)	0.831
Macrovascular complications:			
Stroke, *n* (%)	11 (17.7%)	8 (13.8%)	0.554
Myocardial infarction, *n* (%)	11 (17.7%)	15 (25.9%)	0.281
Coronary artery bypass graft surgery, *n* (%)	11 (17.7%)	7 (12.1%)	0.384
Overall mortality, *n* (%)	10 (16.1%)	14 (24.1%)	0.273

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EP354

Cardiovascular risk factors associated with diabetic nephropathy

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Introduction

Diabetes is the leading cause of end-stage renal disease. Renal disease is a cardiovascular morbidity and mortality predictor which is three times more common in diabetic patients with diabetic nephropathy (DN). We aim to describe the factors of cardiovascular risk associated with DN in a group of type 2 diabetes patients.(T2D).

Materials and Methods

It was retrospective and descriptive study including 204 patients with T2D and confirmed DN, hospitalized in the Internal Medicine at UHC "Mother Teresa", between January to December 2021.

Results

There were 97 (47.5%) women and 107 (52.5%) men with mean age was 70.93 $\pm$ 9.64 years. The body mass index was 28.98 $\pm$ 6.24 kg/m^2. The average duration of diabetes was 11.35 $\pm$ 5.32 years. In 87.7% of cases, treatment for diabetes was insulin therapy. Microalbuminuria as incipient nephropathy was present in 104 patients and 100 patients had renal failure with GFR <90 ml/min. High blood pressure was present in 144 patients, 88% of whom were on ACE inhibitors. Other microangyopathic complications were present, such as diabetic retinopathy in 13.7% patients, 6 of which had a proliferative form and peripheral neuropathy in 25% patients. Ischemic heart disease was found in 36.6% of patients and angiopathy of the lower limbs in 11 patients. Hypertriglyceridemia was observed in 97 patients, hypo-HDL-cholesterolemia in 24 patients and hyper LDL-emie in 75 patients. 69.7% of patients had hiperuricemia. We noted a positive correlation between the DN stage and the severe of glycated hemoglobin (P0.002), as well as duration of diabetes. However, no significant correlation has been demonstrated between the micro and macro albuminuria and the triglyceride level, HDL cholesterol and the LDL cholesterol level.

Conclusions

Diabetic nephropathy increases the cardiovascular risk in T2D. Its prevention and management, requires an optimal glycemic and blood pressure control, in order to protect not only the kidney but also to reduce cardiovascular risk and thus to improve the quality of life of diabetics and their prognosis of life.

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EP355

Effects of hypertension on the degenerative complications of diabetes

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Introduction

High blood pressure and type 2 diabetes are two pathologies that are often closely linked. The objective of our work is to determine the prevalence of hypertension and its effects on degenerative complications in a type 2 diabetic population.

Methods

This is a retrospective study including 147 patients, followed at the Tunis National Institute of Nutrition for type 2 diabetes and comorbidities.

Results

The mean age of the patients was 57.52 $\pm$ 11.96 years with 66.7% women ($n=98$). The duration of diabetes was 11.42 $\pm$ 8.58 years. Average fasting glucose was 13.76 $\pm$ 5.15 mmol/l. Half had retinopathy (52.1%), one-third had neuropathy (33.3%) and 28.3% had diabetic nephropathy. Coronary insufficiency, peripheral artery occlusive disease (PAD) and stroke were found in 15.5%, 6.9%, and 4.8% of cases, respectively. High blood pressure was noted in 60.5% of patients. Its presence was positively correlated with age ($P<0.001$) and the duration of diabetes ($P<0.001$). The average fasting glucose was higher in hypertensive patients, but not significantly so ($P=0.89$). Retinopathy and neuropathy were more noted in the presence of hypertension ($P=0.2$ and $P=0.12$ respectively). The latter was significantly associated with diabetic nephropathy ($P=0.02$). It was also more frequent in the presence of coronary insufficiency ($P=0.002$). Hypertensive diabetics were also at greater risk of developing stroke or PAD ($P=0.2$ and $P=0.7$ respectively).

Conclusion

Hypertension was common and significantly associated with diabetic nephropathy and coronary insufficiency in our sample, hence the need for its early detection.

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EP356

A Case Report: Why Continuous Glucose Monitoring in Conjunction with the GluCare. Health Care Model is Important in a Patient Newly Diagnosed with Type 2 Diabetes

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Introduction
Hypoglycaemia is one of the most important acute complications of diabetes. The fear of hypoglycaemia has a significant effect on the quality of life of patients and their families. It also remains a major barrier to achieve optimal glycaemic control. The GluCare Health care model is centered on the use of Continuous Metabolic Monitoring (CMM) and behavioural change to address metabolic diseases in a continuous manner. The Glucare program aims to provide continuous patient supervision and support through personalized lifestyle coaching and behavioural change and includes the use of wearables and continuous glucose monitors (CGM).
Case Report
A 42-year-old male patient presented with symptoms of polyuria and polydipsia. He was diagnosed with type 2 Diabetes Mellitus in another center. He had been advised empagliflozin/ metformin and insulin for diabetes management. Patient refused to use insulin and visited our clinic for his long-term treatment plan. His blood glucose: 109 mg/dl, HbA1c was 10%. There was nothing significant in his physical examination. Tirzepatide 2.5 mg/week, Empaglifozin/Metformin twice daily and onboarding into the GluCare platform was advised to him. In his follow up, after 14 days, according to his food logging and CGM data he received feedback from the dietician, diabetes educator and exercise / sleep recommendations from the health coaches. In the third week of his follow up, although it was not expected, he started to observe low blood glucose values in CGM which was also confirmed with a home blood glucose measurement device. Tirzepatide stopped and continued with empagliflozin/ metformin. Patient did not experience hypoglycaemia anymore. During his follow up his time in range was 95% and glucose management indicator was 5.9%.
Discussion/Conclusions
In a conventional healthcare model, patients with diabetes are evaluated episodically with both engagement and data gaps occurring between scheduled patient visits. Diabetic patients, especially those newly diagnosed, can be better managed when using platforms such as GluCare Health which includes the continuous monitoring and engagement of patients by their care team. CMM generates personalized data and is utilized by care teams to provide the necessary insights to help educate patients about their lifestyle choices and behaviour, in addition to evaluating medication choices, in a hyper-personalized manner to avoid non-compliance with treatment. Long term randomized controlled trials needed to evaluate the effect of CGM in conjunction with the GluCare.Health Care Model to prevent acute and long-term complications of diabetes.

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EP357

Prevalence and Predictors of Chronic Complications of type 2 Diabetes Mellitus; our experience

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The prevalence of type 2 diabetes (T2D) is rapidly increasing. Diabetes is a silent disorder leading to disabling and fatal complications. The long-term complications of diabetes affect almost every system in the body, especially the eyes, kidneys, heart, feet and nerves. Our aim was to examine the global prevalence and major risk factors for microvascular complications among people with T2D hospitalized in Internal Medicine.
Methods
We conducted a retrospective cohort study among patients hospitalized with T2D in one year. We evaluated these patients for microvascular complications, such as nephropathy, retinopathy, neuropathy, as well as for comorbidities.
Results
A total of 204 participants were included in this study. The mean age of participants was 70.93 ± 9.2 years old. 107 (52.5%) male and 97 (47.5%) woman. 13.7% of patients had diabetic retinopathy, 64.7% diabetic nephropathy and 25% diabetic neuropathy. There was a significant statistical relationship between these complications and HbA1C, as well as longer duration of diabetes. The most common concomitant diseases were: hypertension with a prevalence of 94.1%, dyslipidemia with a prevalence of 36.3% and CHD with a prevalence of 36.3%. Regarding the treatment of diabetes, 87.7% of patients were under treatment with insulin therapy and 15.7% with oral antidiabetics.
Conclusion
The prevalence of chronic complications was higher. Longer duration of diabetes, and poor glycemic control were predictors of chronic diabetes complications. Hypertension was the most frequent comorbidity in diabetic patients and the presence of hypertension accelerates the development of microvascular complications. It is important to achieve good glycemic control and manage comorbid diseases, to minimize the risk of chronic diabetes complications.

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EP358

Gamma-GT blood levels and chronic complications of type 2 diabetes

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Objective
Our objective was to determine the relationship between mean blood gamma-GT (GGT) levels and chronic complications of type 2 diabetes.
Patients and Methods
This was a descriptive study including 89 diabetic patients followed at the department A of the National Institute of Nutrition in Tunis.
Results
The mean age was 56.44 ± 13.02 years. The mean GGT level was 54.77 ± 61.13 IU/l. Diabetes was uncontrolled in 93% of cases with a mean HbA1C of 10.7%. Diabetic retinopathy, nephropathy, and neuropathy were noted in 43%, 19%, and 26% of cases, respectively. Macroangiopathic complications were dominated by coronary artery disease (17%). The analytical study showed a statistically significant association between plasma GGT concentration and the presence of diabetic retinopathy ($P = 0.026$). Plasma GGT concentration was also higher in nephropathy and neuropathy ($P = 0.13$ and $P = 0.15$ respectively) but not significantly. Coronary and arterial patients had higher mean GGT ($P = 0.43$ and $P = 0.4$ respectively). The same was true for patients with a history of stroke, and significantly so ($P = 0.017$).
Discussion
GGT would induce an increase in oxidative stress and lipid accumulation in hepatocytes, thus leading to insulin resistance in hepatocytes[1]. It would therefore be a possible biomarker for the detection of diabetic complications.
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EP359

Severe infections revealing type 2 diabetes: Epidemiological, clinical and therapeutic aspects

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Introduction
Type 2 diabetes is an important risk factor for all forms of infection. It may be unrecognised for many years, and often revealed by degenerative or infectious complications. The aim of this study is to investigate the epidemiological, clinical and therapeutic aspects of severe infections revealing type 2 diabetes.
Patients and Methods
Retrospective descriptive cross-sectional study of a series of 5 patients with severe infections revealing type 2 diabetes.
Outcomes
The mean age of our patients was 44.8 years [33-49 years], with a 60% female predominance (3/5). The mean hemoglobin A1c at the time of diagnosis was 11.1% [8-14.3%]. Infections were: Kidney abscess, breast abscess, diabetic foot with phlegmon, pyo-pneumothorax, severe pneumonia. Ketoacidosis or ketosis decompensation was associated in 60% (3/5) of cases. The therapeutic management differed according to the type of infection. All patients had broad-spectrum intravenous antibiotic therapy and received insulin therapy. Discussion: Type 2 diabetes can remain silent for many years, often revealed by degenerative or infectious complications. It is an immunocompromising condition that predisposes to infections in all its sites. This appears to be related to deficits in the immune system, particularly changes in innate immunity. Respiratory infections, cutaneous and soft tissue infections, gastrointestinal and genitourinary infections all appear to occur more frequently in people with diabetes. Not only are they more frequent, but these infections seem to have a poorer response to treatment and a more rapid progression to severe forms of infection.
Conclusion
Infections revealing type 2 diabetes are common, and routine screening for diabetes in patients with severe or recurrent infections is necessary.

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EP360

Hyperglycemia-induced hemichorea in a Diabetic patient with accompanying post stroke seizure: A case report

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Background
Non-ketotic hyperglycemia hemichorea is a movement disorder characterized by irregular, involuntary and abrupt hyperkinetic movements caused by hyperglycemia. The pathophysiology remains unclear however there are several theories on its mechanism. The diagnosis is confirmed by presence of involuntary irregular movements combined with findings of hyperdensities on the basal ganglia in cranial computed tomography scan (CT-scan) or magnetic resonance imaging scan (MRI) .Pharmacologic goals of treatment include control of hyperglycemia and involuntary movements with several medications including anti-psychotics, GABA-receptor agonists, selective serotonin reuptake inhibitors or dopamine-depleting agents.
Case Presentation
A 74-year-old male known diabetic was admitted with complaints of involuntary movements on the left extremities accompanied by right sided facial spasms. The patient presented with elevated blood glucose on admission with a random blood sugar of 439 g/dl and an HbA1c level of 13.2%. He was admitted as a case of a post stroke seizure versus cerebrovascular infarct with poorly controlled Type 2 Diabetes Mellitus. A cranial computed tomography (CT-scan) was done which showed hyperdense lesions on the right caudate head. The post-stroke seizure was also confirmed by the presence of epileptiform discharges from the right frontal region on electroencephalogram (EEG). The patient's treatment focused on blood glucose control and anti-seizure medications. There was resolution of symptoms after blood glucose was controlled.
Conclusion
Nonketotic-Hyperglycemic hemichorea is a rare and poorly understood neurologic complication of Diabetes Mellitus. Control of blood glucose combined with pharmacologic therapy to control involuntary movements remain superior in management of symptoms with good prognosis.

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EP361

Shingles manifesting as a vesicular rash only on the foot: A case report

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Background
Shingles is dermatomal vesicular rash secondary to reactivation of latent varicella zoster virus. It is well recognized when it appears on the trunk, neck or face. Herpes zoster can be easily overlooked in case of dermatomal rash in lower extremity.
Observation
A 32-year-old diabetic female was hospitalized for diabetic ketoacidosis. She had trouble walking because of painful rash on the plantar surface of the right foot. She reported the development of a burning pain one day before the eruption. Crops of vesicular rash were present on the plantar surface of the right foot at the initial visit. A sensation of burning pain preceded the onset of the rash. These symptoms led to the diagnosis of herpes zoster. Antiviral local agent of valacyclovir was administered for 7 days. Skin lesions resolved within two week. She recovered from post herpetic neuralgia three months later.
Conclusion
Acute painful limb or new neurological complaint requires a thorough physical examination with skin assessment. Atypical dermatomal skin lesions may appear in second place suggesting the diagnosis of herpetic neuralgia. Apart from trunk, neck or face herpes zoster can manifest as a dermatomal rash in the lower extremity. Fatal consequences can take place if the diagnosis is missed and early treatment isn't instituted.

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EP362

Predictive factors for the onset of urinary disorders in patients with diabetes mellitus: A case-control study

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Objective
To assess the predictive factors for the occurrence of urinary dysfunction (UD) in patients with diabetes mellitus (DM).
Patients and Methods
Case-control study comparing two groups of patients suffering from DM: G1 ($n=159$) with UD vs G2 ($n=41$) without UD.
Results
G1 patients were older than G2 patients (59.7 ± 10.3 vs 58 ± 12 years) with no significant difference in gender. The duration of diabetes was significantly longer in G1 (11.9 vs 7.7 years; $P=0.03$). G1 patients were significantly more frequently insulin-requiring (62% vs 42.5%; $P=0.025$) but with an obvious delayed switch to insulin than G2 (7.6 vs 2.6 years; $P=0.011$). Mean HbA1C was statistically significantly worse in G1 (9.5% vs 8%; $P=0.01$). Microvascular complications were more reported in G1 ($P=0.021$). Macroangiopathy did not appear to be associated with UD in our series ($P=0.07$). The multivariate analysis identified long-standing diabetes (OR=1.07; $P=0.033$; CI95%=[1.01-1.16]), HbA1C> 7% (OR=0.38; $P=0.045$; CI95%=[0.15-0.57]) and peripheral neuropathy (OR=6.43; $P=0.000$; CI95%=[2.39-17.28]) as independent predictive factors for the development of UD in patients presenting with DM.
Discussion
A preventive strategy against the onset of UD in patients with DM should be considered by acting on modifiable predictive factors. The pillars of this strategy would be earlier detection of diabetes, more effective glycaemic control, timely use of insulin therapy, and delaying the onset of chronic complications.
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EP363

Microbiocenosis state in patients with type 1 Diabetes Mellitus

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Introduction
Diabetes Mellitus (DM) is one of the Global pandemics despite to new knowledges and methods of prevention and therapy intensively increased among children, adolescents and adults. Many studies shown the role of the gastrointestinal microbiocenosis in the development and clinical future of DM. Gut microbiota produce numerous bioactive molecules, which can act locally and secreted into bloodstream. The aim of our study were evaluation of gut microbiota in children and adolescent with DM1.
Material and Methods
In 54 patients with MD1, 21 boys and 33 girls in age from 6 to 18 years old blood fasting glycemia, HbA1c level were measured; gut microbiome status were estimated by number of E.coli, lactobacillus, staphylococci, mycobacterium in feces using PCR.
Results
Fasting glycemia level in patients were varied between 5.9 and 13.1 and HbA1c level were 12.9 ± 0.3%. Results of studying the violation of gut microbiocenosis in children with type 1 diabetes showed decrease in the total number of anaerobes and active reproduction of aerobes, including opportunistic pathogens. Thus, they had a deficiency in the total number of anaerobes, bifidobacteria and lactobacilli were found in 100% of cases ($P < 0.01$). At the same time, the content of almost all aerobes significantly increases, especially lactose-negative Escherichia coli, fungi of the genus Candida and Proteus - 6.86 ± 0.165; 6.21 ± 0.28; 4.8 ± 0.32 lg CFU/g, respectively. The most characteristic decrease in the number of lactose-positive Escherichia coli to 6.75 ± 0.59 lg CFU/g against the basic increase in the content of lactose-negative Escherichia coli, enterobacteria, staphylococci, fungi of the genus Candida, especially Proteus ($P<0.001$). Dysbiotic changes in most cases were accompanied by the isolation of bacteria of the opportunistic pathogenic group. Intestinal microflora had differences depending on the duration of the disease and dysbiotic changes were more pronounced in those with disease duration more than 6 years, than those with less than 3 years.
Conclusion
Gut microbiocenosis were changed in patients with DM1 where disbiotic changes shown in decreasing of anaerobes and increasing of aerobes, including opportunistic pathogens. Gut microbiome state may reflected on glycemia level and depends from duration of diabetes.

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EP364

Erectile dysfunction: An early warning sign of urinary disorders in men suffering from diabetes

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Objective
To determine the prevalence and analyze the predictive value of erectile dysfunction (ED) in the occurrence of fictional disorders (MD) in men with diabetes mellitus (DM).
Patients and Methods
Cross-sectional study of 90 men presenting with DM. A comparative analysis was performed between two subgroups: G1 ($n=75$) with MD vs G2 ($n=15$) without MD.
Results
G1 patients were older than G2 (59.7 ± 10.3 vs 58 ± 12 years). The duration of diabetes was significantly longer in G1 (11.9 vs 7.7 years; $P=0.03$). G1 had poorer glycaemic control than G2, as the mean HbA1C was statistically more impaired in G1 (9.5% vs 8%; $P=0.01$). Microvascular complications were more frequent in G1 ($P=0.021$), notably diabetic retinopathy ($P=0.07$), diabetic nephropathy ($P=0.02$), and peripheral neuropathy ($P=0.000$). Diabetic macroangiopathy was not associated with urinary disorders ($P=0.07$). There was a significantly higher prevalence of ED in G1 (23.3%) compared to G2 (7.5%); $P=0.021$. Multi-variate logistic regression confirmed that ED was an independent predictor of MD in men with DM with an Odds Ratio of 3.61 ($P=0.005$; 95% CI=[0.95-13.74]). Discussion: ED and MD are two manifestations of diabetic dysautonomia secondary to alteration of the autonomic nervous system and bladder-sphincter dyssynergia. ED, an earlier condition, should prompt the clinician to screen for and treat possible underlying urinary disorders.
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EP365

Co-occurrence of diabetic ketoacidosis and acute pancreatitis in patients with type 1 diabetes mellitus: Clinical and biological peculiarities

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Objective
To describe the clinical and biological presentation of acute pancreatitis (AP) and diabetic ketoacidosis (DKA) in type 1 diabetes (T1D).
Patients and Methods
A retrospective descriptive study of 10 T1DM patients with simultaneous DKA and AP.
Results
The mean age at diagnosis of T1DM was 19.7 ± 9.3 years with a female predominance (60%). T1DM was frequently inaugurated by a cardinal syndrome (50%) or spontaneous DKA (20%). In 10%, T1DM was diagnosed at the time of AP. The mixed AP-DKA episode occurred at a mean age of 26.9 ± 14.9 years. A febrile state (30%) with altered general condition (20%) and severe dehydration (10%) was often reported. Respiratory and neurological signs were present in 20%. Digestive signs were prominent, notably epigastralgia (90%), vomiting (50%), and diarrhea (20%). Acetonuria was massive in 50% with mean blood glucose levels of 3.2 ± 1.4 g/l. Metabolic acidosis was noted in all cases with mean pH and bicarbonate values of 7 ± 0.3 and 12.3 ± 8.3 respectively. Functional renal failure complicated the course of 10% of cases. An infectious syndrome accompanied 40% of cases with a mean CRP of 47 ± 72.9 mg/l. The evolution was favorable in all patients after appropriate treatment with an estimated insulin requirement of 0.76 ± 0.3 IU/kg/d.
Discussion
The co-occurrence of DKA and AP in T1DM is a relatively rare but potentially serious event due to the mutually deleterious effects of these two conditions. The outcome of this mixed emergency depends on early diagnosis and prompt intervention.
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EP366

Diabetic peripheral neuropathy: Prevalence and predictive factors

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Introduction
Diabetic peripheral neuropathy (DPN) is a frequent complication of diabetes mellitus. The aim of our work is to determine the prevalence as well as the predictive factors of this degenerative complication and as a secondary endpoint the evaluation of the risk factors associated with painful diabetic neuropathy.
Methods
This is a retrospective and prospective cross-sectional study with descriptive and analytical aims conducted over a period of 4 years between January 2018 and October 2022 in the department of endocrinology and metabolic diseases of the Ibn Sina University Hospital in Rabat as well as the consultation center. Patients with type 1 diabetes with less than 5 years of evolution, secondary diabetes, and patients with gestational diabetes were excluded. Sociodemographic, clinical and biological parameters as well as degenerative complications were collected using a predefined questionnaire. Univariate and multivariate statistical analysis were performed using JAMOVI 2.3.18 software. The significance threshold was set at the conventional value of 0.05.
Results
We included 250 diabetic patients, from which 207 were found to have type 2 diabetes mellitus. The mean age of our patients was 55.2 years ±14.8 years. The overall prevalence of diabetic peripheral neuropathy was found to be 26.8% of. 71 patients (28.4%) were found to have painful diabetic neuropathy. The multivariate logistic regression analysis revealed that the factors significantly associated with diabetic peripheral neuropathy were: diabetes duration ≥10 years (OR= 7.42; IC95%: 1.49-36.83, $P=0.01$), and sedentary lifestyle (OR= 10.64; IC95%: 2.28-49.57; $P=0.003$). On the other hand, the factor significantly associated with neuropathic pain was: sedentary lifestyle (OR= 6.43; IC95%: 1.55-26.65, $P=0.01$).
Conclusion
Our study underlines that the duration of diabetes and sedentary lifestyle are risk factors for the occurrence of diabetic peripheral neuropathy and neuropathic pain. Particular attention should be paid to the interest of regular screening as well as physical activity in order to relieve diabetic patients and improve their quality of life.

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EP367

The reliability of ankle brachial index measurement in screening for peripheral arterial disease

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Introduction
The peripheral arterial disease is a serious complication of diabetes. Although frequent, it is often underestimated in our diabetic patients.
Goal of the Study
The aim of our study is to verify the validity of ABI measurement in the screening of PAD in diabetic patients.
Patients and Methods
Retrospective, descriptive and analytical study taking place over a period of 3 years, including 120 diabetics, where doppler ultrasound was performed in the face of suggestive symptoms or as part of an arterial assessment. The measurement of the ABI was carried out in all our patients. Data entry and statistical analysis was done using IBM SPSS software.
Results
The average age of our patients was 57.3 years, where type 2 diabetes predominated in 83.4% of cases with an average duration of evolution of 17 years, the average HbA1c was 9.8%. The major risk factors for atherosclerosis found in

our patients were dyslipidemia in 43.3%, hypertension in 28.3%, obesity in 26.6% and smoking in 16.6%. The trophic disorders were objectified in 31.6% of our patients and the pulses were weakly perceived in 35.8% of the patients, 40% of the patients reported intermittent claudication. The ankle brachial index was measured in both limbs with an average ABI of 0.94, it was pathological in 66.6%. An ABI < 0.9 was found in 51.6% of patients and an ABI > 1.3 in 15%. The PAD objectified corresponding to a pathological arterial Doppler ultrasound was 84.1%. Atheromatous overload was objectified in 39.1%, 9.1% had arterial stenosis and 15.8% had arterial mediacalcosis. A significant relationship was found between the ABI and the doppler ultrasound of the lower limbs with a $P=0.003$. For the validity of the IPS, the sensitivity was 72.3% and the specificity was 63.2%, the PPV was 91% and the NPV was 30%.

Conclusion

Given its silent nature, peripheral arterial disease is often underdiagnosed in diabetics, resulting in a delay in diagnosis and management. The ankle brachial index remains a reliable way to detect and assess the severity of PAD.

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EP368

Impact of glycemic and blood pressure control on diabetes management during the covid-19 pandemic and social isolation

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For the first time in Georgia (Ajara) has been started in parallel two research populations in with the management of diabetes and its complications during social isolation under the conditions of the Covid 19 pandemic. The research (PHDF-22-2943) is carried out with the financial support of Shota Rustaveli National Science Foundation.

Aim

The aim of the study is to compare ,How adequately used blood glucose and blood pressure control at home, the opinion of diabetic patients and doctors regarding the management of the disease during the covid-19 pandemic in the conditions of social isolation.

Material and Methods

a cross-sectional study design with a special questionnaire was used. Two survey forms were developed for Doctors and for Patients with diabetes. Both questionnaires were converted to the Microsoft form format. The study began in October 2022. So far, 220 Patients with diabetes and 72 doctors have participated in the survey.

Results and Discussion

According to preliminary data, it was found that, although 97% of patients have a personal glucometer and tonometer. During the isolation 11% of patients did not monitor blood glucose level, 33% tested once a week, 11% once a day, 44% several times a day; According to doctors opinion, 3% of patients did not test for blood glucose, 42% tested once a week, 21% once a day, 34% several times a day. Glycemic ranged between 140-250 mg% was 72% in the group of patients and 84.5% cases in the group of doctors. In the group of patients, 19.5% did not test their blood pressure. High BP up to 150 mm/hg was 39% of patients were observed in the group of doctors 69%. According to the doctors, medical intervention was needed 13% for angina pectoris attack, myocardial infarction 8%, heart failure 8%, arterial hypertension 43%, hyperglycemia 7% hypoglycemia 2%; among the patients in 13% cases heart attack, high blood pressure 22%, hyperglycemia 8%, kidney stones 2%. In both groups, there was insomnia in the group of patient 56% and in the group of doctor 62%, as well as anxiety in the group of doctors 82%, in the group of patients 58% and Feeling of loneliness 28%.

Conclusion

Inadequate glycemic and blood pressure control in diabetic patients increases the risk of developing cardiovascular disease and subsequent death, especially during emotional instability and isolation. It is necessary to increase the patient's awareness about blood pressure and glycemic control in order to prevent complications.

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EP369

Prevalence and determinants of hypophosphatemia during the treatment of diabetic ketoacidosis

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Introduction

Diabetic ketoacidosis (DKA) is an extreme metabolic state caused by insulin deficiency. Hypophosphatemia in DKA often occurs during hospitalization. The aim of this study was to determine the prevalence and determinants of hypophosphatemia during the treatment of diabetic ketoacidosis.

Methods

This is a retrospective cross-sectional descriptive study concerning all patients hospitalized in the Endocrinology Department for DKA between October 2021 and January 2022. Glycemia at presentation and phosphatemia levels during treatment were determinated on AU 680® Beckman Coulter. Glycosylated haemoglobin (HbA1c) levels were determined on ADAMS ® ARKRAY at presentation. Hypophosphatemia was defined as measured serum phosphate less than 0.8 mmol/l. The treatment phase was defined as 1.5 hours from admission to the end of the treatment.

Results

A total of 30 patients were hospitalized for DKA. The mean age of the group was 26.73 $\pm$10.41years, 60% (18/30) of the cases was female. Type 1 diabetes was observed in 63.3% of patients. There were 33.4% newly diagnosed diabetes. Phosphore levels were measured during the treatment phase in 21 cases. The mean phosphate levels was 0.877 mmol/l (range 0.2 to 1.59; SD $\pm$0.37). Hypophosphatemia ($<$0.8 mmol/l) was present in 33% (7/21) and severe hypophosphatemia ($<$0.32 mmol/l) in 14% (3/21). None of the patients suffered from symptoms related to hypophosphatemia. Means glycemia and HbA1c in the group who presented hypophosphatemia and for the group with normal phosphate during the treatment were similarly high 23.52 $\pm$ 18.44 mmol/l; 13.45 $\pm$ 1.92% and 18.26 $\pm$ 7.46 mmol/l; 12.86 $\pm$ 3.08% ($P=0.29$; $P=0.334$) respectively. Means of duration of insulin therapy were 40.42 $\pm$ 20.44 hours and 31.12 $\pm$ 20.36 hours ($P=0.85$) respectively for the group who presented hypophosphatemia and for the group with normal phosphate during the treatment. The group who presented hypophosphatemia during the treatment received statistically similar total insulin dose infusion 80.85 $\pm$40.88 units vs 62.25 $\pm$40.72 units; ($P=0.85$).

Conclusion

Hypophosphatemia was present in 33% of patients with DKA during treatment The systematic and repeated measurements of phosphate levels are necessary in monitoring patients during treatment.

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EP370

The dietary survey, an unreliable tool for assessing the authentic nutritional status in elderly patients with diabetes mellitus

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Objective

To test the reliability of the classic diabetic survey (DS) in the diagnosis of malnutrition in elderly patients with diabetes mellitus (DM).

Patients and Methods

Analytical study of 55 patients aged over 65 years who were hospitalized in the Endocrinology Department. A DS was performed for all patients. The diagnosis of malnutrition was established according to the criteria proposed by the HAS 2021. Two subgroups were compared: G1 ($n=18$) undernourished seniors. G2 ($n=30$) non undernourished senior.

Results

The mean age of the included seniors was 71.4 $\pm$ 6.6 years with a female prevalence (53.7%). Very old patient with DM ($>$ 70 years) represented 46.3% of our population. The mean HbA1C level was 11.2 $\pm$ 3.2%. Significant glycaemic imbalance (HbA1C $>$ 10%) was reported in 77.8% of cases. The majority of patients were treated with insulin (84.9%). The mean BMI was 26.7 $\pm$ 5.5 kg/m^2. The mean daily energy intake was slightly lower in G1 without statistical significance. The ROC curve study of the DS variable shows an area under the curve of 0.62 with CI95% = [0.44-0.81]. The DS is thus an unreliable tool for determining the nutritional status of elderly patients with DM with a very poor sensitivity (57.7%) and specificity (40%).

Discussion

Malnutrition is a pathology that accompanies and aggravates the various geriatric syndromes. The daily caloric intake estimated by a classic DS does not indicate the nutritional status of elderly patients with DM. To better detect malnourishment in the geriatric population, we recommend the use of more reliable clinical tools such as the Mini-nutritional Assessment (MNA) score.

References
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EP371

Assessment of nutritional status in in-patients with diabetic mellitus using Nutritional Risk index

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Background
Patients with Diabetes Mellitus (DM) are exposed to malnutrition, due to dietary restrictions and associated conditions. However, in daily practice, malnutrition is often under-diagnosed among these patients.
Aim
To assess the risk of malnutrition in patients with DM admitted to an Endocrinology Department using the Nutritional Risk Index (NRI).
Methods
We conducted a cross-sectional study to calculate the NRI in patients with DM admitted to the Endocrinology department between March and September 2020. We used the formula NRI= (1.489×serum albumin) +41.7×(actual weight/usual weight). Patients were considered in no risk of malnutrition if NRI >100. Patients with NRI between 97.5-100 and 83.5-97.5 were considered in mild and moderate risk of malnutrition respectively. Patients with NRI less than 83.5 are in risk of severe malnutrition.
Results
In total, 106 patients with DM were admitted. Among them, 67 patients (63.2%) reported loss of weight, but in only 28 patients (26.4%), the maximal weight could be determined. The Mean weight upon admission was 70 +- 14.95 kg, the mean loss of weight was 12.07+-6.35 kg. The mean usual body weight was 82.09 +- 14.8 kg. The median NRI was 88.45 [80.2-89.14]. According to the NRI, 16 patients (57.1%) were considered in moderate risk while 11 patients (39.3%) were considered in the high risk group. Only one patient was considered in no risk of malnutrition.
Discussion and conclusion
Our results show the frequency of malnutrition among patients with DM. in fact, approximately two thirds (63.2%) of admitted patients with DM report loss of weight. Those with loss of weight were mostly in moderate or high risk of malnutrition. These results emphasize the need to incorporate assessment of nutritional status in diabetic patients in daily practice to prevent and manage malnutrition in a timely manner.
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EP372

This study compared the impact of TGC beginning during surgery versus after surgery on postoperative adverse events in individuals undergoing heart surgery

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Introduction
During the perioperative period, surgical operations put patients under a great deal of physical stress. The immune system produces cytokines and other immune mediators in response to this threat. Recent studies have shown that using insulin to regulate blood glucose can reduce systemic inflammation.
Objective
The objective of this research was examined how postoperative intensive insulin treatment (IIT) affects the inflammatory response in a synthetic pancreas during heart surgery with cardiopulmonary bypass.
Method
Two groups of patients undergoing cardiopulmonary bypass surgery were formed: the IIT group ($n=15$) and the conventional treatment (CT) group ($n=15$). At the start of surgery, an artificial pancreas was used to manage blood glucose in the IIT group. The blood sugar level was kept at 110 mg/dl for 20 hours after surgery. To track changes in serum cytokine levels over time, blood samples were taken. The mean±standard deviation was used to express all data. The nonparametric test (Mann-Whitney U-test) was used to assess the data for single comparisons. It was deemed statistically significant when $P<0.04$ was used.
Results
The characteristics of the patients were similar between groups. After surgery, blood glucose levels were much higher in the CT group. Interleukin-6, high-mobility group box 1, and tumor necrosis factor- serum levels were all greater in the CT group than in the IIT group.
Conclusion
During the postoperative period, IIT was safely performed during cardiac surgery with cardiopulmonary bypass utilizing an artificial pancreas. IIT also showed anti-inflammatory properties. An artificial pancreas used in conjunction with intensive insulin therapy has the potential to be a useful way to manage blood sugar during surgery, which would reduce the risk of both perioperative and postoperative problems. The inflammatory response was significantly reduced during the perioperative period when IIT was used in the artificial pancreas. Additionally, no signs of hypoglycemia was found in individuals receiving IIT. This shows that patients who are severely unwell may benefit from the safe and efficient use of IIT in a synthetic pancreas.
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EP373

Lipid profile of postmenopausal women

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Aim of the Study
The main objectives were to examine the incidence of hyperlipoproteinemia in postmenopausal women and to determine the differences in lipid profile considering age, duration of menopause and body mass index in postmenopausal women.
Material and Methods
The research was structured as a cross-sectional research with historical data. The research used data collected during regular check-ups in primary health care clinics in the Osijek Health Center, Croatia, from November 2021 to March 2022. Collected data were: demographic data, information on the duration of menopause, body mass, body height, body mass index, values of total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides and data on associated diseases.
Results
The study included 98 postmenopausal women, median age of 68. The median duration of postmenopause was 17 years. Statin therapy was used in 40.8% of respondents. Over 50% of respondents had elevated total cholesterol values (median: 5.60 mmol/l) and LDL cholesterol values (median: 3.25 mmol/l). 39.8% of respondents had elevated triglyceride values (median: 1.50 mmol/l). The values of total cholesterol (Kruskal Wallis test, P0.001) and LDL cholesterol (Kruskal Wallis test, P0.01) were significantly higher in the group of respondents aged 45 to 64 years, compared to older respondents. No significant differences were found in lipid profile in relation to the duration of postmenopause and the body mass index. Using the SCORE2 table, it was estimated that 65% of the respondents had a very high cardiovascular risk and 24% of them had a high cardiovascular risk. Only 6% of the respondents achieved the target values of LDL cholesterol. Respondents who did not reach the target values were significantly older (Mann Whitney U test, P0.01) and for a longer period of time in menopause (Mann Whitney U test, P0.009) compared to the respondents who achieved the lipid profile target values. No association of body mass index with the achievement of lipid profile target values was found.
Conclusion
Incidence of hyperlipoproteinemia in postmenopausal women is very high. Age and duration of menopause have an impact on the poorer achievement of the target values of the lipid profile. Given the high prevalence of respondents with a very high cardiovascular risk intensive interventions are needed at all levels of health care which include non-pharmacological and pharmacological methods of treating hyperlipoproteinemia.
Keywords: cardiovascular risk score; hyperlipoproteinemia; HMG-CoA reductase inhibitors; postmenopause
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EP374

Atherogenic Index of Plasma Associated Cardiovascular Risk in 10,241 Paediatric Patients

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Background
Cardiovascular disease (CVD) is a leading cause of mortality. Childhood obesity is a major contributor to CVD. Atherogenic index of plasma (AIP) is an indicator of risk of atherosclerotic CVD. Associations between childhood obesity and CVD risk in the region remains under-explored. We aim to investigate this association as a predictor of CVD in this young population.
Methods
Patients who attended our Centre (2009-2019), age $\leq$19 years and with complete lipid profiles were assessed. Extracted data was grouped per sex, age and BMI percentile: normal-weight (NrWt) 5th – 85th percentile, overweight (OvWt) 85th – 95th percentile and obese (Ob) 95th percentile. AIP was calculated using the logarithmic formula, log(Triglyceride(TG)/high-density lipoprotein cholesterol (HDL-C)) [1]; patients were divided into three risk groups (Gps): Gp1 = low, Gp2 = intermediate and Gp3 = increased CVD risk.
Results
In our study population (n = 10,241), 52.9% of total patients were females. Female percentage is different in each AIP risk group: Gp1 = 59.6%, Gp2 = 46.5% and Gp3 = 35.4% in low, intermediate and high risk groups respectively. In the different BMI percentiles, CVD risk varied; 88.00%, 8.75% and 3.25% in Gp1 (low), Gp2 (intermediate) and Gp3 (high) respectively. In the overweight/obese (OvWt/Ob) group specifically, 41.3% of patients were in Gp1 (low risk), 72.7% of patients were in Gp2 (intermediate risk) and 81.4% were in Gp3 (high risk).
Conclusion
Even at a young age, all patients displayed some level of AIP associated CVD risk. There is a significant group of children and adolescents with increased risk of cardiovascular disease who do not belong to familial hypercholesterolemia group. This is further exacerbated by obesity. The data highlights the importance of early identification of these patients at a younger age, potentially earlier than previously acknowledged to prevent long-term detrimental complications.
Reference
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Table 1 Cardiovascular risk in paediatric patients

Categories		Atherogenic Index of Plasma (AIP) -Logarithmically Transformed Ratio of Molar Concentrations of Triglycerides to HDL-Cholesterol		
		Gp1 Low Risk (AIP $<$0.1)	Gp2 Intermediate Risk (AIP 0.1 - 2.1)	Gp3 Increased Risk (AIP $>$2.1)
Patient Number (*n*)	Total *n*	9012	896	333
	Females	5373 (59.6%)	417 (46.5%)	118 (35.4%)
	Males	3639 (40.4%)	479 (53.5%)	215 (64.6%)
Weight (BMI Percentile)	Total *n*	9012 (88.00%)	896 (8.7%)	333 (3.3)
	NrWt	4546 (50.4%)	227 (25.3%)	60 (18.0%)
	OvWt	3720 (41.3%)	651 (72.7%)	271 (81.4%)
	UnWt	746 (8.3%)	18 (2.0%)	2 (0.6%)

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EP375

Statin Treatment in Children and Adolescents with Elevated LDL-c in Patient with Normoglycaemia and Dysglycaemia

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Background
The obesity prevalence surge in children and adolescents is associated with dysglycaemia, dyslipidaemia and long-term cardiovascular complications. Use of lipid-lowering medications[1] has been recommended following lifestyle modifications. We aim to investigate the demographic, and changes in LDL-c, in these young patients, in the presence and absence of dysglycaemia.
Methods
Complete lipid profiles of patients ($\leq$19 years old) with hyperlipidaemia who are prescribed statin therapy was extracted based on International Classification of Diseases (ICD) Codes (n = 150). Patients with familial hypercholesterolemia (n = 20), or prescribed Omega-3 supplements (n = 61), were excluded. The remaining patients (n = 69) were further sub-grouped per sex and diabetes status. Median (IQR) LDL-c levels were calculated with Wilcoxon matched-pairs signed rank test for Pre- and Post-statin therapy (6 months) initiation was analysed using GraphPad PRISM 9 with statistical significance set at the $\leq$0.05 level.
Results
Within the study population (n = 69 patients) receiving statin therapy (females = 51.43%), mean age was 15.97 $\pm$ 3.02 years (minimum = 6 years; maximum = 19 years). Sub-grouped per diabetes status; normoglycaemic (NGT; n = 15 [21.7%]), Pre-Diabetes (Pre-Dia; n = 10 [14.5%]), type 1 diabetes (T1DM; n = 33 [47.8%]), type 2 diabetes (T2DM; n = 8 [11.6%]), MODY (n = 2, 3.0%) and secondary diabetes (n = 1; 1.4%). Median (IQR) LDL-c levels for all patient groups significantly decreased compared to baseline; *P*-value 0.01 - $<$0.0001.
Conclusion
All patients receiving statin therapy, independent of their diabetes status, showed a significant decrease in LDL-c levels post-statin therapy. Data further highlights the importance of identifying young patients where lifestyle modifications alone is not effective particularly in the presence of obesity and/or diabetes. This indicates that early detection, diagnosis, and timely intervention in management of dyslipidemia, is cornerstone in avoiding long-term cardiovascular disease in young patients. Patients (n = 61) were assessed Pre- and Post-lipid lowering (statin) therapy. Median (IQR) LDL-c levels were calculated with statistical significance ($\leq$0.05 level).
Reference
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Table 1 LDL-c changes in children and adolescents with hyperlipidaemia

LDL-c Level (mmol/l)	Patient Groups	Pre-statin therapy	Post-statin therapy (6 months)	Change in Statin (ΔLDL-c mmol/l)	*P*-value
	All Patients	4.60 (3.92, 5.19)	3.52 (3.00, 4.42)	1.08	$<$0.0001
	NGT	5.00 (4.11, 546)	4.00 (3.22, 5.00)	1.00	0.001
	Pre-Dia	4.57 (3.96, 4.96)	3.88 (2.94, 4.67)	0.69	0.002
	All NGT + Pre-Dia	4.84 (4.08, 5.18)	4.00 (3.22, 4.99)	0.84	$<$0.0001
	T1DM	4.56 (3.85, 5.53)	3.36 (2.99, 4.43)	1.20	$<$0.0001
	T2DM	3.89 (3.38, 4.71)	3.53 (2.14, 422)	0.36	0.008
	All Dia	4.46 (3.72, 5.30)	3.38 (2.95, 422)	1.08	$<$0.0001

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EP376

Berberine vs Pioglitazone: Management of NAFLD and its Impaired Glucose Metabolism

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This study aimed to determine if berberine (BBR) or pioglitazone (PGZ) is more effective and safer for treating people with type 2 diabetes or non-alcoholic fatty liver disease (NAFLD). 184 people with NAFLD and impaired glucose metabolism were randomly allocated 16 weeks of lifestyle intervention (LI), LI plus PGZ (15mg daily) or LI plus BBR (1.5 g daily) as their course of treatment. We measured the levels of blood insulin, osteocalcin, C reactive protein (CRP), liver enzymes, glucose and lipid metabolism, and hepatic fat content (HFC) by 1 H-MRS both before and after treatment. In comparison to LI alone, BBR plus LI treatment was linked to significantly greater decreases in HFC (51.30% vs 27.98%), triglycerides, total cholesterol, waist circumference, body weight, alanine aminotransferase (ALT), as well as significant elevation in early phase insulin and serum osteocalcin levels. In terms of 2-hour glucose and ALT, PGZ plus LI considerably outperformed LI group, while the difference in HFC between PGZ and control was not statistically significant (41.02% vs 27.98%). Fasting glucose, LDL-c, HDL-c, HbA1c, glutamyl transferase, serum CRP levels, and aspartate aminotransferase, improved more in the LI + BBR or PGZ group than in the LI group, but the differences between the groups were not statistically significant. There were substantial differences in the incidence of drug-related adverse events between groups. LI, LI + BBR, or LI + PGZ are all successful treatments for NAFLD patients with aberrant glucose metabolism in terms of improving glucose metabolism, lowering HFC, and lowering liver enzymes. The lipid profile, early phase insulin secretion, weight loss, reduction in waist circumference, and serum osteocalcin levels were all improved by BBR more than the other two therapies. All of BBR and PGZ were accepted.

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EP377

Familial chylomicronemia syndrome: A case report

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Background
Familial chylomicronemia syndrome is a rare disorder of lipoprotein metabolism with an incidence of one per million in the general population. It is characterized by marked elevation of triglyceride and chylomicron levels, resulting in lipemic plasma and recurrent attacks of acute pancreatitis, eruptive xanthoma, hepatosplenomegaly, and lipemia retinalis.
Case Presentation
We report the case of an 18 years old patient, an only son ,from a cansanguineous marriage of 2nd degree with a personal history of 4 episodes of acute pancreatitis since the age of 4 months, who presents a lipemic fasting blood and a lipid profile with triglyceride levels over 15000 mg/dl, a normal cholesterol and a low high-density lipoprotein (HDL) levels .Physical examination was insignifcant for any findings. There were no eruptive xanthomas or abdominal pain. Abdominal ultrasound was normal. The lipid profile of his father shows a moderate hypertriglyceridemia at 2860 mg/dl, the mother assessement was normal.Familial chylomicronemia syndrome was diagnosed. Our patient was given a special diet devoid of triglyceride and containing medium chain fatty acid diet and was also started with fenofibrate and omega 3. After a month, repeated blood test revealed a reduction in triglyceride level to 3100 mg/dl.
Discussion and Conclusion
Familial chylomicronemia syndrome is an autosomal recessive disorder resulting from lipoprotein lipase (LPL) or apolipoprotein C-II deficiency or due to the presence of an inhibitor of LPL. The diagnosis of familial LPL deficiency is based on the demonstration of lipemic plasma with elevated chylomicron and triglyceride levels and a reduced to normal VLDL level, and is confirmed by assessment of LPL activity in plasma. Familial apolipoprotein-CII deficiency shows a raised VLDL level in addition to the derangements as seen in LPL deficiency. Acute relapsing pancreatitis is the most significant and often life-threatening complication. Dietary modification plays a key role in the management of this disease. Dietary fat should be restricted to <20 g/day and $<15\%$ of the total caloric intake so that triglyceride levels are maintained below 1500 mg/dl. Fibric acid derivatives and omega 3 are recommended. Fenofibrate may reduce hepatic triglyceride synthesis and increase LPL activity. Adverse effects of fibrates include elevated creatinine kinase and liver enzymes. Volanesorsen are new therapeutics that reduce triglyceride levels to less than 750 mg/dl in 77% of patients with familial chylomunclonemic syndrome. thrombocytemia and injection site reactions were common adverse effects.
Keywords: Chylomicronemia, Lipoprotein lipase ,acute pancreatitis .
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EP378

Efficacy and durability of a very low calorie ketogenic diet protocol on metabolic parameters

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Metabolic Syndrome (MetS) is characterized by the association of insulin resistance, hypertension, dyslipidemia, non-alcoholic fatty liver disease, and is strictly related to increased cardiovascular risk. Recent scientific evidence confirms that very low calorie ketogenic diet (VLCKD) is a valuable treatment for patients with insulin resistance and visceral obesity. After the VLCKD phase it is essential to gradually reintroduce carbohydrates and increase calories in order to switch towards a Mediterranean nutritional approach. The aim of this study was to evaluate the efficacy and durability of a VLCKD protocol on cardiometabolic parameters related to MetS. Twentynine patients with MetS, obesity and insulin resistance [12 males and 17 females, homeostatic model assessment index (HOMA) ≥ 2.5, age 56.7 ± 6.4 years, body mass index (BMI) 35.3 ± 3.9 kg/m^2)] followed a VLCKD for 45 days (≤ 800 kcal/day). After the VLCKD phase (45 days), they followed a low calorie diet (LCD, 1100-1200 Kcal) with a low carbohydrate content (60-80 g/day) for 45 days. Subsequently, patients were switched to a hypocaloric Mediterranean diet (HMD-1500 Kcal) with 120-130 g/day carbohydrate content and monitored for additional 60 days (150 days). Anthropometric indexes, blood and urine chemistry, and body composition were assessed. Body weight [-8.7 ± 3.3, $P<0.001$], BMI [-3.2 ± 1.0 kg/m^2, $P<0.001$], blood pressure (-9.1 ± 14.2 mmHg, $P=0.002$], waist circumference [-6.4 ± 3.0 cm, $P<0.001$], HOMA index [-4.3 ± 5.8, $P<0.001$], insulin [-13.6 ± 14.4 µIU, $P<0.001$], total and low-density lipoprotein cholesterol (LDL) [-49.5 ± 31.2 mg, $P<0.001$; -36.7 ± 20.6 mg, $P<0.001$ respectively] and triglycerides [-65.9 ± 93.6 mg, $P<0.001$] markedly decreased in all participants during VLCKD phase (day 45). Importantly, body weight [-3.5 ± 1.7 kg, $P<0.001$], BMI [-1.3 ± 0.6 kg/m^2, $P<0.001$], total and LDL cholesterol [-21.4 ± 20.8 mg, $P<0.001$; -19.2 ± 17.2 mg, $P<0.001$, respectively] showed a further significance decrease during LCD phase (day 90), as compared to the end of VLCKD phase. Noteworthy, a significant reduction of visceral adipose tissue (VAT) was observed at the end of VLCKD phase [-103.5 ± 128.7 cm^3, $P<0.001$], as well as the end of LCD phase [-80.5 ± 120.3 cm^3, $P=0.002$]. Importantly, a trend in body weight reduction [-0.6 ± 1.5 kg, $P=0.125$] was observed at the end of HMD phase (day 150), compared with the end of LCD phase (day 90). Our study confirms that VLCKD protocol is an effective strategy in the management of obesity and its metabolic comorbidities, due to its pleiotropic effects, particularly on the reduction of visceral adipose tissue. Indeed, favourable effects on body weight and metabolic risk factors persist also after the reintroduction of carbohydrates and the switch to a HMD.

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EP379

Does prebiotics consumption improve glycemic parameters in obese adults?

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Background
Alteration of gut microbiota leads to increased intestinal permeability, inflammation, and metabolic disorders. The aim of our study was to determine the effect of prebiotic supplementation on glycemic parameters in addition to a weight loss program.
Methods
This is an interventional study including 30 obese patients consulting the obesity unit of the Institute of Nutrition in Tunis. The patients were divided into 2 groups matched for age, sex and BMI: diet alone and prebiotics (30g of carob/day). Glycemic parameters (fasting blood glucose, HbA1c, fasting insulin levels and HOMA index= insulin resistance score) were assessed at T0 and at one month after the intervention (T1).
Results
The mean age was 40.3 $\pm$6.7years with sex ratio Male/Female $=0.25$. Diabetes was found in 6.7% of patients in the diet alone group and 26.7% of patients in the prebiotic group (the difference between the two groups was not significant $P=0.3$). There was no significant difference between the two groups for glycemic parameters at T0 (fasting blood glucose, HbA1c, fasting insulin levels and HOMA index). For the diet alone group, there was a significant decrease in HbA1c between T0 and T1 ($P=0.03$). For the prebiotic group, we found a significant decrease in insulin levels ($P=0.002$) and insulin resistance score ($P=0.009$). A statistically significant difference between the diet alone group and the prebiotic group was found for the decrease in fasting blood glucose (0.01), insulin levels ($P=0.03$) and insulin resistance score ($P=0.01$).
Conclusion
Prebiotics are superior to diet alone in improving the glycemic profile. Thus, they therefore have their place in the therapeutic arsenal of pre-diabetes and diabetes in obese patients.

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EP380

Relationship between nutritional screening CIPA and sarcopenia in hospitalized patients

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Introduction
Malnutrition and sarcopenia are interrelated and frequent in hospital settings, being related to a higher morbimortality. CIPA nutritional screening (performed at the Hospital Universitario Nuestra Señora de Candelaria) is positive when one or more of the following criteria is met: a) decreased oral intake in 72 h (<50%), b) albumin <3 g/dl, and c) BMI <18.5 g/m^2 or mid-upper arm circumference (MUAC) ≤ 22.5 cm.
Aim
To determine the relationship between the results of CIPA screening and the diagnosis of sarcopenia in hospitalized patients.
Method
Single-center, cross-sectional study. Hospitalized subjects >18 years old who underwent CIPA malnutrition screening were included. Loss of muscle mass was measured by bioimpedanciometry (appendicular skeletal muscle mass, ASMI), and strength by handgrip measure. Sarcopenia was established according to the EWGSOP2 diagnostic criteria.
Results
332 patients were analyzed. The mean age was 66.04 ±14.41 years (52.1% men). Distribution by specialties is shown in table 1. CIPA was positive in 36.1% (criteria why CIPA was positive are shown in Table 2), while 19.9% of the whole sample had sarcopenia. 33.3% of positive CIPA patients had sarcopenia vs 12.3% of negative CIPA ($P<0.0005$). The positivity of the CIPA variables BMI/MUAC (31.8% vs 16.5%; $P<0.0005$) and oral intake control (35.8% vs 16.8%; $P=0.001$) correlated with the presence of sarcopenia. The trend to significance was observed with the positivity of albumin (27.8% vs 17.7%; $P=0.058$).
Conclusions
in this cohort of patients a positive CIPA nutritional screening test is related to a higher prevalence of sarcopenia, so it represents a valid tool to identify patients with the highest risk of morbimortality.

Table 1 Distribution by specialties

Admissions by specialty	*n*	%
Internal medicine	46	13.9
General surgery	28	8.4
Vascular surgery	12	3.6
Gastroenterology	54	16.3
Haematology	11	3.3
Nephrology	24	7.2
Pneumology	42	12.7
Oncology	24	7.2
Neurology	39	11.7
Traumatology	41	12.3
Cardiology	11	3.3
Total	332	100

Table 2 Positive CIPA criteria

CIPA criteria	*n*	%
None	212	63.9
BMI	14	4.2
Albumin	51	15.4
BMI + albumin	2	0.6
Oral intake	32	9.6
Oral intake + BMI	2	0.6
Oral intake + albumin	15	4.5
All of them	4	1.2
Total	332	100

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EP381

Metabolic effects of caffeine consumption in obese patients

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Background and Aim
Coffee is consumed worldwide and have been an important aspect of societal norms and cultural traditions for centuries.The health effects of routine caffeine consumption and their potential function as modifiable risk factors for cardiovascular disease have recently been the suggested by many studies. The aim of this study is to evaluate the daily caffeine consumption in obese patients and its clinical and metabolic effects.
Methods
This is a cross-sectional study conducted in 70 obese patients. Patients' demographic and anthropometric characteristics, obesity related complications and biological parameters were collected. Insulin resistance was estimated by HOMA-IR index. Metabolic syndrome was defined according to the International Diabetes Federation criteria (2009). Caffein daily consumption was evaluated depending on the average quantity of coffee and the type of coffee consumed according to the international caffein organization[1]. Low caffeine consumption was defined by an average consumption of less than 200 mg per day,a consumption of caffeine between 200 and 400 mg per day defined a moderate consumption and high caffeine consumption was defined as a daily intake of more than 400 mg. In this study we combined moderate and high caffeine consumption to improve precision of estimates.
Results
Mean age was 50.91±11.5years with female predominance(90%).Mean Body mass index (BMI)was 39.42±6.47 kg/m^2, mean waist circumference was 118.95±11.04 cm. Of the study population, 22.9% of patients had class 1 obesity,38.6% of patients had class 2 obesity and 37.1% had morbid obesity. Insulin resistance was noted in 87.5% of cases and more than half of patients had metabolic syndrome (65.7%). Coffee was consumed on a daily average of 193±73.42 ml, which was equivalent to an average of 133.96±85.95 mg of caffeine per day. Caffeine intake was minimal, moderate, and high in 81.2%, 17.1% and 1.4% of cases, respectively. Patients with minimal caffeine intake had a significantly higher prevalence of metabolic syndrome compared to patients with moderate to high caffeine intake (61.4% vs 4.3%; $P=0.001$). Prevalence of nonalcoholic fatty liver disease and insulin resistance did not statistically differ between the two groups. Systolic and diastolic blood pressure values, total cholesterol,triglyceride,HDL-c and LDL-c levels did not statistically differ between the two groups.
Conclusion
Moderate to high habitual consumption of caffeinated beverages is safe across a broad range of cardiovascular conditions.Our findings support the hypothesis on the possible health benefits of caffein consumption particularly on metabolic syndrome, yet further research on large-scale studies is needed.
Reference
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EP382

Evaluation of the results of weight loss at 5 years after bariatric surgery at the Regional Hospital of Málaga

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Introduction
Morbid obesity is a highly prevalent disease, with bariatric surgery being a fundamental pillar in its treatment.
Objectives
To analyze the results of weight loss at 5 years in patients operated by gastric bypass and sleeve at the Regional University Hospital of Malaga.
Methods
This is a retrospective observational study, where 104 patients with morbid obesity who underwent bariatric surgery at the Regional University Hospital of Malaga between 2011 and March 2017 were analyzed.
Results
The mean age at the intervention was 46.6 years (19-67), 77 women and 27 men, 41 were operated by bypass and 63 by sleeve. The mean baseline weight was 131.1±26.4 kg with a mean BMI of 48.9±7.7 kg/m^2. 56.8% had a BMI between 40-50 kg/m^2, 7.8% between 35-40 kg/m^2, 24.5% between 50-60 kg/m^2 and 9.8% had a BMI above 60 kg/m^2. The average weight at one year of the intervention was 86.6 kg, at 2 years 84.8 kg, at 3 years 88.7 kg, at 4 years 91.1 kg, and at the fifth year, the mean weight was 95 kg. The percentages of excess weight lost were also calculated, at one year it was 71.8%, at 2 years it was 73.6%, at 3 years it was 66.4%, at 4 years it was 63.6% and at 5 years it was 59.0%. Likewise, the percentage of patients who had lost more than 50% of the excess weight they had prior to surgery was obtained: at one year it was 88.3%, at 2 years it was 90.0%, at 3 years it was 77.3%, at 4 years it was 78.9% and at 5 years it was 66.3%.
Conclusions
Satisfactory weight results are observed 5 years after bariatric surgery, achieving a loss above 50% of excess weight in 66.3% of patients.

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EP383

Association between sleep duration and sociodemographic characteristics, mental health and chronic diseases in obese adults

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Background
Sleep is crucial for brain function, productivity, physical and mental well-being. The objective of our work was to examine the relationship between short sleep duration and its associated factors (sociodemographic characteristics, mental health and chronic diseases) in adult individuals with obesity.
Methods
Cross sectional study, including 100 obese adult patients consulting the Obesity Unit of the National Institute of Nutrition in Tunis in 2022. Exclusion criteria: patients with shift work or night work, psychiatric illness, neuroleptic medication or any medication that may interfere with sleep. Data were collected during one-to-one interviews. Sleep duration was self-reported. Sleep duration <7 hours/day was considered as short. Sociodemographic characteristics and medical history were also collected. Screening for anxiety and depression was performed using the HAD questionnaire.
Results
Mean age was 46.7 ± 12.3 years with a sex ratio M/F 0.3. Almost half of the women (52.6%) were menopausal. Our patients were professionally active in 47% of the cases but only 22% of the participants had a higher education level. The majority of our study population (70%) belonged to the middle socioeconomic class and 73% were married. Half of the patients (54%) had a low level of physical activity. The mean BMI was 40.3 ± 6.6 kg/m^2 with class III obesity in 46% of cases. Complications of obesity in descending order were: sleep apnea syndrome (83%), hypercholesterolemia (64%), hypertension (48%), prediabetes (41%), gastroesophageal reflux disease (31%), diabetes (30%), hyperuricemia (29%), hypertriglyceridemia (28%), osteoarthritis (15%), and cardiovascular disease (7%). we found a high prevalence of anxiety (41% of patients had doubtful to certain symptomatology) and depression (42% of patients had doubtful to certain symptomatology). Mean sleep duration was 7 h:16 ± 1 h38 and 46.7% of patients had short sleep duration (<7 h/day). Analytical study showed that Short sleep duration was significantly associated with low socioeconomic level ($P=0.014$), diabetes ($P=0.014$), anxiety ($P=0.005$) and depression ($P=0.031$).
Conclusion
Poor socio-economic conditions represent a source of stress that affects sleep duration. Besides, obese population is at high risk of psychological complications that in return affect sleep.

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EP384

What is the impact of prebiotic supplementation on anxiety symptoms and stress levels in obese patients?

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Background
Obese population is at risk of psychological complications such as anxiety and depression. We carried out this study to assess the effect of a weight loss program and prebiotic supplementation on anxiety symptoms and stress levels in an obese adult population.
Methods
Interventional study involving 30 obese patients consulting the obesity unit of the National Institute of Nutrition in Tunis between June and August 2022. Patients were divided into 2 groups matched for age, sex and BMI: diet alone and prebiotics (30 g carob/day). All patients were screened for anxiety symptoms using the HAD score (anxiety dimension). The Cungi stress scale was used to evaluate stress level. The two questionnaires were administered at T0 and one month after the start of the diet (T1).
Results
The mean age was 40.3 ± 6.7 years with a female predominance (80% of women). There was a significant weight loss in each group (diet only group: -2.5 kg $P=0.001$ and prebiotic group: -2.2 kg, $P=0.003$). However, there was no significant difference between the two groups ($P=0.7$). For the diet alone group, at T0, anxiety related symptoms were present in 100% of the patients (13.3% doubtful symptoms and 86.7% certain symptoms). For the prebiotic group, anxiety related symptoms were present in 80% of patients (13.3% doubtful and 66.7% certain) but no statistically significant difference between groups was found ($P=0.4$). More than half of the study population (73.3%) had a high to very high level of stress (80% of diet alone group vs 66.6% of prebiotic group) but no statistically significant difference between groups was found ($P=0.7$). At T1, there was a significant improvement in the HAD-anxiety scores for both groups: diet alone group (mean difference (T0-T1) $=2.1$, $P=0.02$) and prebiotic group (mean difference (T1-T0) $=1.9$, $P=0.01$). Likewise, we have noticed a significant improvement in the Cungi stress scale scores for both groups: diet alone group (mean difference (T0-T1) $=6.7$, $P=0.01$) and prebiotic group (mean difference (T0-T1) $=4.8$ $P=0.001$). There was no significant difference between the two groups for the improvement of anxiety symptoms or stress level between T0 and T1 ($P=0.8$ and $P=0.5$ respectively).
Conclusion
Our study showed a high prevalence of psychological distress among obese patients. The improvement in anxiety symptoms and stress levels was not related to prebiotic consumption. This improvement is more related to the weight loss.

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EP385

A secular trend in childhood obesity: Post-COVID statistical analysis

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Introduction
Childhood obesity has reached epidemic levels in developed as well as in developing countries. According to WHO data, an increasing number of low- and middle-income countries are now facing the "double burden" of obesity and overweightness. This problem is increasing aggressively in urban settings. This rise has occurred similarly among boys and girls. In 2016, 18% of girls and 19% of boys were overweight. In comparison, two data illustrate the pandemic scale of childhood obesity growth: just under 1% of children and adolescents aged 5–19 were obese in 1975, while more than 124 million children and adolescents (6% of girls and 8% of boys) were obese in 2016. A study conducted by The National Institute of Endocrinology Tbilisi, Georgia has identified additional childhood epidemic outbreak linked with post-COVID lifestyle.
Methods and Materials
The target group was 828 children aged 5–8 years who underwent medical and physical examinations during ambulatory visits to The National Institute of Endocrinology clinics in 2021 and 2022. Children with congenital disease and/or birth weights lower than 2500 g were excluded. Only the information collected during the first visit was used to evaluate the post-COVID effect on childhood obesity statistics. The collected data included age, gender, and anthropometric characteristics. Statistical analyses were performed using the electronic health system Doctra Enterprise, version 8.3.19.1150. BMI-for-age percentile was calculated based on CDC growth charts for children and teens aged 2 through 19 years (3).
Results
The medical records for 730 patients aged 5–8 years, of which: 426 were girls and 304 were boys, were analyzed. During 2021, from 326 evaluated patients, 50.92% ($n=166$) had healthy weights, 13.49% ($n=44$) were overweight, 30.06% ($n=98$) were obese, and 2.45% ($n=8$) were underweight. During 2022, from 404 evaluated patients, 42.07% ($n=170$) had healthy weights, 15.34% ($n=62$) were overweight, 37.62% ($n=152$) were obese, and 4.95% ($n=20$) were underweight.
Conclusions
There has been a significant increase in the incidence of obesity among children. A limitation of this study was the small number of participants and scope of the inquiry. However, the spike in overweight and obesity cases indicates as yet unknown changes caused by the COVID-19 pandemic. Several studies are currently being conducted by The National Institute of Endocrinology in Tbilisi, Georgia to determine the root cause of the current spike.

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EP386

Evaluation of the ratio of C-reactive protein to prealbumin (CP ratio) as a diagnostic tool for malnutrition. transversal study

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Introduction
Disease-related malnutrition (DRM) is characterized by the presence of an acute or chronic inflammatory response. The traditional parameters for diagnosis, such as albumin, have failed in their application, forcing a reconsideration of the criteria used for the diagnosis of DRM. The ratio of C-Reactive Protein to prealbumin (CP ratio) allows to assess nutritional changes in relation to the inflammatory environment. The objective of this study is to assess the diagnostic capacity for malnutrition of CP ratio, correlating it with GLIM criteria.
Material and Method
Cross-sectional pilot study in hospitalized patients, under follow-up by the Nutrition Unit of Hospital La Paz. Patients with inflammation, diagnosed by C-Reactive Protein (CRP) > 0.5 mg/dl, were included. CP ratio was measured in the initial evaluation and compared with isolated prealbumin for the clinical assessment of malnutrition. ROC curves were used in the statistical analysis.
Results
91 patients were included, 65 with DRM (28 with severe DRM) based on GLIM criteria. The CP ratio presented an area under the curve (AUC) = 0.556 (95% CI: 0.420-0.691) for the diagnosis of malnutrition versus normally nourished; and AUC = 0.552 (95% CI: 0.408-0.696) for the diagnosis of severe versus moderate DRM. Prealbumin presented an AUC = 0.536 (95%CI: 0.402-0.671) for the diagnosis of malnutrition versus normally nourished and AUC = 0.551 (95%CI:0.407-0.694) for severe versus moderate DRM. When comparing CP ratio with prealbumin alone, there were no significant differences in the ability to detect DRM($P = 0.880$) or severe DRM ($P = 0.992$).
Conclusions
The CP ratio has poor diagnostic accuracy for DRM and the degree of malnutrition. It does not show superiority with respect to prealbumin in patients with inflammation.

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EP387

Effect of the integration of the weight loss protocol of the endocrinology service in the follow-up of patients with severe osahs and obesity at the Juan Ramón Jiménez hospital

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Introduction
Obstructive sleep apnea-hypopnea syndrome (OSAHS) and obesity are two pathologies increasingly prevalent in population related to each other. Obesity is present in between 60-90% of patients diagnosed with OSAHS being the most important modifiable risk factor. Obesity influences the risk factor for OSAHS degree of severity, increasing its severity by up to 30%. The degree of relation between both pathologies, we created a protocol Endocrinology and Pneumology services, searching the effect on weight loss in our patients.
Material and Methods
Descriptive, retrospective, cross-sectional study. We incluided 70 patients diagnosed with severe OSAHS (apnea-hypopnea index -AHI- greater than 30) and with obesity (BMI greater than 25 kg/m^2). 35 patients received a basic intervention in nutrition and dietetics and another 35 received the recommendations included in the weight loss protocol created by the Endocrinology service. We compared weight loss one year after the nutritional intervention.
Results
Between the patients who received a basic intervention in nutrition and diet, 79.4% were men and 20.6% were women. 44.1% (p 0.033) of these patients had been diagnosed with Type 2 Diabetes Mellitus; 17.6% of the patients had previously presented an ischemic cardiovascular event and had an average BMI of 34 kg/m^2. 11.8% of the patients (P: 0.045) had lost weight one year later with an average of 34 kg. The patients who received the protocol guideline created by the Endocrinology Service, 90.3% were men and 9.7% women. 19.4% (P 0.033) had been diagnosed with Type 2 Diabetes Mellitus and they had an average BMI of 35 kg/m^2. 32.3% of the patients (P 0.045) had lost weight one year later with an average of 31 kg.
Conclusions
The weight loss applying the Endocrinology service protocol was statistically significant (P 0.045) in our study, observed in 32.3% of the patients to whom said protocol was applied, compared to the application of a basic intervention, where a weight loss of 11.8% (P: 0.045) is observed.

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EP388

Neck circumference and metabolic syndrome: A cross-sectional study

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Background and Aim
Metabolic syndrome (MetS) is a complex disorder that increases the risk of cardiovascular diseases. Neck Circumference (NC) can estimate the subcutaneous upper body fat distribution which has been recognized as associated with MetS. The aim of our study is to investigate the possible association of NC with cardiometabolic risk factors and MetS and to determine the possible cutoff points of NC for the diagnosis of MetS.
Methods
This is a cross sectional study including 60 obese patients. Diagnosis of MetS was based on the International Diabetes Federation 2009 criteria. Clinical characteristics, anthropometric measures (BMI, waist circumference and NC) were collected. Fasting plasma glucose, HDL-cholesterol (HDL-C), triglyceride (TG) levels, systolic and diastolic blood pressure were assessed. We used ROC curve analysis to estimate the optimal sex-specific NC cut-off point in the diagnosis of MetS.
Results
Mean age was 48.1 ± 15.46 years with female predominance (68.4%).Type2 diabetes mellitus and hypertension were noted in 77.1% and 41.3% of cases. Mean BMI was 32.1 ± 8.1 kg/m^2, mean waist circumference was 106.4 cm ± 14.63 for men and 110.4 cm ± 19.62 for women. Mean NC was 40.3 cm ± 3.7 for men and 38 cm ± 4.5 for women. MetS was diagnosed in 33 (55%) of patients.NC was shown to be significantly associated with waist circumference ($P < 10^{-3}$), systolic and diastolic blood pressure ($P = 0.03$;$P = 0.02$,respectively), triglyceride levels ($P = 0.04$), fasting plasma glucose ($P = 0.001$), and HDL-C level($P < 10^{-3}$) as well as MetS ($P = 0.03$). After multivariate analysis, NC was an independent factor associated MetS (OR 3.5, 95% CI 1.27- 21.16, $P = 0.02$). The optimal cutoff points of neck circumference in the diagnosis of MetS for women is 34 cm (sensitivity of 70% and specificity 30%) and 38 cm for men (sensitivity of 65% and specificity 35%).
Conclusion
This study supports that NC is an effective anthropometric indicator associated with MetS. It has been suggested that more studies should be conducted to analyze the predictive effect of the combined application of anthropometric indicators currently in use and NC.

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EP389

Sleep quality in patients with obesity: what is the association?

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Introduction
Obesity and unhealthy eating pattern have been associated with altered sleep quality. We aimed to assess the sleep quality in a population of obese patients.
Methods
This cross-sectional study included 45 patients who consulted the obesity unit of the National Institute of Nutrition in Tunis. The sleep quality was assessed *using the Pittsburgh Sleep Quality Index (PSQI*, which defines a poor sleeper profile for a score ≥5 points. *Sociodemographic data and anthropometric measures were collected.*
Results
The average age was 46 years (14-79) with a female predominance (80%). The average weight was 99 ± 20 kg with an average Body mass index (BMI) of 37 ± 6 kg/m^2 and an average waist circumference of 116 cm (89-170). Overall, 51% of the subjects were good sleepers (PSQI < 5) while 49% were poor sleepers (PSQI ≥5). Better sleep quality was positively associated with physical activity ($P = 0.003$). Poor sleepers, when compared to good sleepers, had significantly higher weight (108 ± 16 kg vs 88 ± 19 kg, $P < 0.001$), BMI (39.5 ± 5.5 kg/m^2 vs 36 ± 6 kg/m^2, $P = 0.04$), and waist circumference (123 ± 16 cm vs 109 ± 12 cm, $P = 0.003$). Good sleepers had lower systolic arterial tension (117 ± 14 mmHg vs 133 ± 16 mmHg, $P = 0.002$), and better glycaemic profiles (fasting blood glucose measure = 7 mmol/l vs 8 mmol/l with $P = 0.07$ and HbA1C = 6% vs 7% with $P = 0.1$).
Conclusion
In conclusion, poor sleepers had higher BMI and waist circumference and lower systolic arterial tension. Physical activity was correlated to better sleep quality.

These results highlight that sleep assessment should be an integral part of the management of obesity in order to improve the quality of medical care.

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EP390

Obesity and obesity-related diseases as a new clinical features in 3q27.3 microdeletion syndrome involving adipoq gene: A case study

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Introduction
Adipose tissue is recognized as an important endocrine organ, secreting many endocrine factors. Adiponectin is the most abundant peptide released into circulation, encoded by ADIPOQ gene localized in chromosome 3q27.3. Adiponectin decreases intracellular ceramide, implicated in insulin resistance, inflammation and atherosclerosis. It stimulates fatty acid oxidation in skeletal muscle and inhibits glucose production in the liver. Hypo-adiponectinemia plays a central role in obesity and obesity-related disease. Since the advent of Comparative Genomic Hybridization Array (CGH-Array), numerous new microdeletional syndromes have been described. Few cases of autosomal dominant 3q27.3 microdeletion syndrome have been described, mostly characterized by intrauterine growth retardation, marfanoid habitus, cranio-facial dysmorphism, intellectual disability, psychosis and mood disorder. We describe a family affected by 3q27.3 microdeletion involving ADIPOQ gene, adding obesity and obesity-related disease to constellation of major clinical findings reported in 3q27.3 microdeletion syndrome.
Case Study
A 21-year-old Caucasian male underwent genetic investigation by CGH-Array during a diagnostic study for familiar schizoid-type personality disorder, cognitive delay, macrocephaly and thickening of skull cap. Array analysis revealed a 1.43-Mb deletion in the long arm of chromosome 3 (3q27.3), including ADIPOQ gene and other two OMIM disease genes (KNG1 and BCL6). The analysis was then extended to parental couple, demonstrating the paternal origin of the rearrangement. Afterwards, same microdeletion was demonstrated in his 26-year-old sister. Deletions were confirmed by fluorescent *in situ* hybridization. All family members shared a complex syndromic clinical spectrum consisting of severe neuropsychiatric impairment, schizoid-type personality disorder, cognitive delay and thickening of skull cap, signs compatible with other clinical findings reported in literature for 3q27.3 microdeletion. No marfanoid habitus was reported, even though all had history of ligament laxity-related disorders. All three members of the family shared moderate-severe hyperphagia, early central obesity, marked hyperinsulinemia, obstructive sleep apnea syndrome, arterial hypertension, dyslipidemia and hepatosplenomegaly with hepatic steatosis, composing a new syndromic frame in the context of 3q27.3 microdeletion syndrome.
Discussion
This new clinical spectrum associated with 3q27.3 microdeletion involving ADIPOQ gene reinforce a suggested role of adiponectin haploinsufficiency in central obesity, atherogenic metabolic status, fat accumulation in the liver and dyslipidemia. A possible role of adiponectin on food intake at hypothalamic level is also suggested. The involvement of adjacent loci and genes, such as OMIM genes, may contribute to these novel features in 3q27.3 microdeletion syndrome. The fewer number of bases involved, 1.43-Mb vs >5-Mb described in literature, could explain the absence of some syndromic features.

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EP391

Metabolic syndrome in postmenopausal women with type 2 Diabetes

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Introduction
The metabolic syndrome is associated with an increased cardiovascular risk. The objective of our study was to describe the metabolic profile of postmenopausal diabetic women and to investigate a link between menopause and metabolic syndrome.
Methods
A retrospective study of 30 postmenopausal women with type 2 diabetes was performed in the Nutrition C department of the national institute of Nutrition Tunisia between January and March 2022.
Results
The average age of the patients was 63.69±8.06 years with extremes ranging from 47 years to 80 years. The average duration of diabetes was 12.3±9.23 years. Seventy-seven percent of patients were treated exclusively with insulin, 6% with oral antidiabetics and 50% with dual therapy. Degenerative complications were represented by nephropathy (42%), neuropathy (21.3%), retinopathy (26%), lower limb arteriopathy (11%) and only 2% had a history of stroke. No coronary artery disease was noted. We noted unbalanced diabetes in 75% of cases with an average glycated hemoglobin of 11.8% ±2.12. Arterial hypertension and dyslipidemia were noted in 62% and 51% respectively. The lipid profile showed the following averages: Total cholesterol 4.91±2.5 mmol/l, HDL-cholesterol 1.3±0.5 mmol/l, LDL-cholesterol 1.5 ±0.62 and triglycerides 1.9±0.96 mmol/l. Obesity was found in 53.6% of women with an average body mass index (BMI) of 34.2±1.2 kg/m^2. The waist circumference varied between 89 and 117 cm with the presence of android type obesity in 89.7%. No statistically significant correlation was found between age at menopause and weight, BMI and waist circumference with respectively (P=0.635; r=-0.05), (P=0.487; r =-0.123) and (P=0.716; r=-0.68).
Conclusion
Hormonal changes are associated with an increased cardiovascular risk which is amplified with the coexistence of a metabolic syndrome ,therefore the need for screening and regular monitoring.

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Effects of an online exercise training on autonomic and metabolic control in children with obesity: A feasibility study

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Exercise is one of the major determinants of a healthy lifestyle, being crucial in childhood as a powerful preventive tool. On the other hand, obesity and arterial hypertension rate has been increasing in children, thus increasing the risk of developing cardiovascular and metabolic diseases in adult life. Of vital importance is the modality and volume of exercise required to get benefits. In this feasibility study 35 obese children were enrolled. Autonomic and metabolic control alongside auxological and lifestyle parameters were assessed before and after a 12-week online exercise training. Participants were subdivided into two groups according to the volume of exercise performed (above or below 1200 MET•minutes/week). This threshold level was obtained in two different ways: in subdivision A the total weekly physical activity volume was considered (i.e., time spent both walking for at least 10 min consecutively and performing structured exercise), while in subdivision B only the weekly volume of structured exercise was taken into account. Only in subdivision B a reduction in arterial pressure percentile as well as an improvement of vagal and metabolic control markers were found. Moreover, this 12-week online exercise training, defined on individual fitness level and progressively adapted as per individual reached goal, proved to be sustainable from both an economical and organizational perspective.

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EP393

Prevalence of obesity and metabolic profile in a group of diabetic patients: About 623 cases

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Introduction
Obesity is the result of an imbalance in the energy balance. It is associated with many metabolic pathologies, in particular type 2 diabetes, which presents a medical and economic challenge throughout the world.
Objective of the Study
The objective of our study was to determine the prevalence of obesity and the metabolic profile in a group of diabetic patients.

Materials and Methods
This is a descriptive cross-sectional observational study including 623 patients followed in the endocrinology and metabolic diseases department of the Ibn Rochd University Hospital in Casablanca in a day hospital or in conventional hospitalization between January 2021 and July 2022. The painful diabetic neuropathy was assessed by the DN4 score. Statistical analysis of the data was performed using SPSS version 25.
Results
We included 623 patients, 63.4% of whom were women. The average age of the patients was 51.4±16.1 years. Diabetes was type 2 for 79.9% of patients. The mean HbA1c was 10.22±2.53%. Among our patients, 30.2% were overweight and 30.4% obese including 19.4% grade 1 obesity, 7.1% grade 2 obesity and 3.9% grade 3 obesity. In our study, 28.9% of patients were dyslipidemic. In bivariate analysis, obesity was higher in patients over 69 years old ($P<0.001$), in men ($P<0.001$), in patients with a university education ($P<0.001$), hypertensive patients ($P<0.001$), dyslipidemics ($P<0.001$), smokers ($P<0.001$) and in patients on insulin. In multivariate analysis, it was associated with gender ($P<0.001$) and arterial hypertension ($P<0.001$).
Conclusion
The frequency of obesity in diabetic patients potentiates cardiovascular risk. This recalls the interest of hygienic-dietary rules, in particular the Mediterranean diet and regular physical activity in these patients.

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EP394

Nutritional follow-up after bariatric surgery

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Introduction
Obesity is known to be a risk factor for chronic conditions such as cardiovascular disease, diabetes, chronic kidney disease, non-alcoholic fatty liver disease and many cancers. The use of surgeries for the treatment of it is increasingly common.
Material and Methods
Retro and prospective study including 09 patients followed for obesity in the department of endocrinology and metabolic diseases of the UHC Ibn Rochd and who benefited from bariatric surgery with metabolic and nutritional management in the perioperative period.
Results
We reported the observations of nine patients. The average age was 39.3 years (32-47). The 9 patients were morbidly obese with an average BMI of 53.9 kg/m^2 (46-78) and a waist circumference of 120 cm. The mean duration of obesity was 17 years. Among the triggering factors: pregnancy, divorce and the peripubertal period. All patients underwent sleeve gastrectomy except one "gastric bypass". The 9 patients were placed on a high-protein diet one week before surgery with postoperative nutritional support and vitamin, iron, calcium and magnesium supplementation. The average weight loss was 33.6% of the initial weight in 1 year. Nutritional complications have been noted such as: anemia, hair loss and dry skin, zinc, vitamin B12, calcium and vitamin D deficiency.
Conclusion
The success of bariatric surgery is conditioned by multidisciplinary care with quality nutritional support before and after surgery, in order to optimize long-term weight loss while avoiding the risk of nutritional deficiencies.

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EP395

Impact of Glucagon-like peptide-1 (GLP-1) receptor agonists on insulin resistance and weight as prevention of type 2 diabetes at overweight and obesity patients

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Introduction
Obesity today is a growing epidemic throughout the world. With weight gain, the risk of type 2 diabetes and hypertension increases. With the approval of GLP-1 RA (semaglutide) by the FDA in June 2021 for weight reduction, a big push was given regarding the possibilities of obesity and especially for people at high risk of developing type 2 diabetes.
Aim
To analyze the impact of semaglutide on insulin resistance and weight loss in patients with prediabetes.
Methods and Material
The study prospective with 24 overweight and obese patients without diabetes and other chronic diseases but with high risk for tipe 2 diabetes because of high insulin resistance. In the study, the treatment period varied from 6-12 weeks. HOMA index and body weight reduction was monitjored. Treatment with semaglutide was done with dozes of 0.25 mg, 0.50 mg and 1 mg s.c. once a week. Each patient is instructed to change the lifestyle such as healthy food and physical activity.
Results
The weight loss of the studied population varied and the longer they took the treatment the weight loos was greater. On average, the weight loss for patients who continued the treatment for more than 3 months was from 3-18% (1-14 kg) as well as a significant decrease in the HOMA index.The side effects that were identified were nausea, vomiting and rarely diarrhea. Such weight loss has also been seen in trial studies such as SUSTASIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes, 1-10 trials), STEP (Semaglutide Treatment Effect in Persons) with Obesity, 1-5 trials) and PIONEER (Peptide Innovation for Early Diabetes Treatment 1-10 trials) after witch FDA approved semaglutide for obesity treatment.
Conclusion
The patients in this study had a decrease weight and an improvement in cardiometabolic factors. The number of such risk factors for cardiovascular and metabolic diseases such as type 2 diabetes makes these medications a priority in clinical practice and the only factor that hinders access is the easy prescription of high-priced drugs on the market. Another benefit of semaglutide in weight management is its long-term use.

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EP396

Cerebellar ataxia and new onset diabetes, clinical case report

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Introduction
High levels of autoantibodies to glutamic acid decarboxylase (GAD-Ab) have been described in multiple conditions such as: stiff-man syndrome, type 1 diabetes mellitus, latent autoimmune diabetes in adults (LADA), patients with auto-immune polyglandular failure and etc. In addition, some of the patients with progressive cerebellar ataxia show high titer of GAD-Ab, it may play a critical role in its development, as these antibodies are involved in the pathogenesis suggesting its auto-immune origin. This is a case report of a patient presenting with cerebellar ataxia with new onset latent autoimmune diabetes in adults.
Case Report
A 32-year-old Georgian woman presented with polyuria, polydipsia and 8 kg weight loss for past 2 months. One year before presentation the patient was diagnosed with cerebellar ataxia and was currently disabled, using cane to walk. For two years before the diagnosis she had complained of progressive gait instability and at the diagnosis brain magnetic resonance imaging showed mild cerebellar atrophy. The patient examination revealed dysarthria, horizontal nystagmus, right side head deviation, motor deficiency in right upper and lower limbs, positive Romberg sign. Routine biochemical studies as well as an immunological screening were performed. The laboratory examination showed marked hyperglycemia, glucosuria, ketonuria and impaired insulin secretion. Farther examination showed high Anti-glutamic acid decarboxylase (GAD) antibodies in patient's serum.
Conclusion
In this case cerebellar ataxia and latent autoimmune diabetes in adults can be related autoimmune conditions.

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EP397

A case report: Empagliflozin-Induced Rhabdomyolysis

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Introduction
Sodium/glucose co-transporter 2 (SGLT2) inhibitors are novel oral hypoglycemic agents that are increasingly used in the management of type 2 diabetes mellitus

(T2DM). They are now recommended as second-line pharmacotherapy (in conjunction with metformin) in patients with type 2 diabetes and established atherosclerotic heart disease, heart failure or chronic kidney disease due to their favourable effects on cardiovascular and renal outcomes. We report a case of a 47-year-old woman who developed rhabdomyolysis after commencing the SGLT2 inhibitor empagliflozin. Case presentation: A 47-year-old female case was followed in the endocrinology clinic for T2DM, hyperlipidemia and chronic renal failure (Cre:1.73 mg/dl, GFR:35 ml/min and spot urine albumin/creatinine ratio:243 mg/g). She had been using linagliptin, insulin detemir, fenofibrate, rosuvastatin, candesartan and acetylsalicylic acid for two years. Empaglifozin was added because of her high HbA1c level (7.8%) and renal dysfunction. The patient presented to the emergency department with the complaint of muscle pain two weeks after starting empaglifozin. Laboratory results showed elevated creatinine kinase (CK) level of 3014 U/l (reference range 0-150 U/l) and increased creatinine level (2.84 mg/dl). Her CK levels were in normal range before empagliflozin treatment. No elevation in troponin levels was observed during follow-up. The patient was hospitalized with a diagnosis of rhabdomyolysis. Intravenous saline infusion therapy was started. Rosuvastatin, fenofibrate and empaglifozin were stopped. During the follow-up, creatinine kinase levels decreased to normal levels and creatinine level regressed to its basal level within a week.
Conclusion
Drug-induced myopathies may present with varying severity, ranging from asymptomatic CK elevation, myalgia to rhabdomyolysis with acute kidney injury. Commonly implicated agents are statins and glucocorticoids. There are few case reports in the literature reporting development of myopathy after empaglifozin treatment with/without statins. On the otherhand, a retrospective study including 2202 cases of myopathy by Alkabbani et al., found that reports of myopathy were not disproportionally higher among those using SGLT-2 inhibitors with statins compared to SGLT-2 inhibitors or statins alone at the class level. Although our patient was using rosuvastatin and fenofibrate which are well-described causes of drug-induced rhabdomyolysis, we thought that empaglifozin might induce rhabdomyolysis because of long-term use of anti-hyperlipidemic drugs and the development of rhabdomyolysis 2 weeks after starting empaglifozin. Since the pathogenesis is not known, further studies are needed to determine the relationship between SGLT2 inhibitors and drug-induced myopathy and clinicians should keep in mind the risk of rhabdomyolysis with increased utilization of these drugs.

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EP398

Watch out! Starvation ketoacidosis mimicking diabetic ketoacidosis

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Background
Starvation ketoacidosis (SKA) represents one of three metabolic acidosis caused by the accumulation of ketone bodies in blood. While easily treated, it is a diagnosis that can be easily mimic diabetic ketoacidosis, particularly in the presence of hyperglycemia[1].
Case
We report a 54-year old female, who had been feeling unwell with ongoing nausea and vomiting, and not eating nor drinking for 5 days. She had a history of alcohol excess but had abstained for some time prior admission, and had an anxiety and depression. Regular medication included mirtazapine and propranolol. Her BM was found 21.8 mmol with positive ketones in urine. Venous blood gas revealed metabolic acidosis. Diagnosis of diabetic ketoacidosis with new onset of diabetes and possible SKA were made. She was managed using the local DKA protocol and saw prompt resolution of her acidosis. This patient also received IV thiamine due to concerns regarding overlap of alcoholic ketoacidosis (AKA). As a result, her HbA1c was 34 mmol and anti GAD antibodies were negative. Thus, DKA was ruled out, and diagnosis of starvation ketoacidosis was finally made.
Conclusion
SKA represents raised anion gap metabolic acidosis caused by the accumulation of ketone bodies in the blood and normal or low glucose levels. The other two causes of a ketoacidosis are alcoholic ketoacidosis and the much more common diabetic ketoacidosis as it was previously thought in this case. As, our patient had severe hyperglycemia, which misdirected us to DKA. Thus importantly consider checking HbA1c to confirm DKA.
Reference
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Localisation of the steroid 5β-reductase in hepatoma cells

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The hepatic enzyme 5β-reductase (AKR1D1) sits at the interface between two metabolic pathways, converting steroid hormones to their inactive 5β-reduced metabolites during steroid clearance, and as a step in the synthesis of bile acids from cholesterol. Both the steroid substrates and the bile acid products of AKR1D1 are potent hormones that regulate hepatic energy metabolism and inflammation. It is not known how these two functions are spatially organised within hepatocytes. The subcellular localisation of steroid metabolising enzymes is thought to have a role in determining their activity and substrate preference. Key bile acid synthesis enzymes upstream of AKR1D1 are localised to the endoplasmic reticulum (ER) membrane and we hypothesised that a fraction of AKR1D1 would localise at the ER to facilitate its role in bile acid synthesis. To test this hypothesis, AKR1D1 tagged with green fluorescent protein (AKR1D1-GFP), or GFP alone, were overexpressed in HepG2 hepatoma cells. The ER was labelled using a targeted red fluorescent protein (ER-RFP). Serial optical sections of cells expressing both AKR1D1-GFP (or GFP) and ER-RFP were imaged using Airyscan laser scanning confocal microscopy, and the 3D colocalisation of the fluorescent probes was quantified using ImageJ. There was no difference in the degree of colocalisation with ER-RFP between AKR1D1-GFP or GFP. These data suggest that AKR1D1 does not localise to the ER more than GFP alone. However, the overexpression of AKR1D1-GFP appeared to disrupt the normal localisation of AKR1D1 and so these results need to be confirmed in cells with endogenously tagged AKR1D1. AKR1D1-GFP was observed in both the cytoplasm and nucleus of HepG2 cells. To confirm whether native AKR1D1 localises to the nucleus, nuclear and cytoplasmic fractions were isolated from HepG2 cells and fraction purity confirmed by Western blot using Lamin A/C and β-Tubulin as controls. AKR1D1 was detected in the cytoplasmic but not the nuclear extract, suggesting that the nuclear staining may be an artefact of overexpression.

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EP400

Circadian profiles of amino acids and biogenic amines in serum and dried blood spot assessed by LC-MS/MS in healthy subjects

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Introduction
Recent studies demonstrated that circulating concentration of many metabolites fluctuates with circadian rhythmicity. However, detailed information on amino acid and biogenic amine daily variations is still lacking. Dried blood spot (DBS) sampling appears to be a convenient tool for studies requiring multiple daily sampling.
Aim
To verify the validity of DBS as a suitable device, we compared serum and DBS levels and changes along the day of a large panel of amino acids and biogenic amines.
Methods
Six healthy normal weight (BMI = 18.5-25.0 kg/m^2) subjects (3/3 men/women) aged 26-50y were enrolled. All had a standard Mediterranean normocaloric diet during the observation and the 6 preceding days. Six paired serum, from venous, and DBS, from capillary, blood sampling were collected 30 min before and two hours after breakfast (07:30), lunch (13:30) and dinner (19:30). Twenty amino acids and 21 biogenic amines were measured by liquid chromatography-tandem mass spectrometry.
Results
All amino acids were measurable in both serum and DBS. Of 21 biogenic amines, 14 could be measured in both serum and DBS. One was only detected in serum. Concentrations of amino acids and biogenic amines were 16.4-796.2 and 0.049–96.2 μM in serum and 18.9–550.9 and 0.17–157.6 μM in DBS, respectively. Among amino acids, 15 were higher and 3 were lower in serum vs DBS (P: <0.001–0.018). Among biogenic amines, 6 were higher and 5 were lower in serum vs DBS (P: <0.001–0.010). Direct correlations between serum and DBS levels were observed for 14 amino acids (P: <0.0001–0.022) and 11 biogenic amines (P: <0.0001–0.047). Strongest correlations were observed for amino acids in leucine (r=0.794), isoleucine (r=0.760), valine (r=0.740) and proline (r=0.739), and for biogenic amines in acetylornithine (r=0.941), creatinine (r=0.655), putrescine (r=0.590) and serotonin (r=0.582). Parallel significant daily variations were observed both in serum and in

DBS for isoleucine, leucine, methionine, phenylalanine, proline, tryptophan, tyrosine, valine and methionine sulfoxide (*P*: 0.001–0.068). The positive quadratic trend indicated higher levels in the morning and evening, and lower levels at midday. Additional significant reduction along the time points was observed in DBS for creatinine ($P < 0.001$) and kynurenine (*P*0.007).

Conclusions

Information conveyed by DBS parallels those by serum for most of the analytes. Furthermore, DBS provided additional evidences on creatinine and kynurenine daily variations. DBS represents a valid opportunity to study amino acid and biogenic amine circadian variations in physiologic and clinical conditions related to the HPA axis.

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Role of selective arterial calcium stimulation test in the evaluation of hypoglycaemia post Roux-en-Y gastric bypass

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We present the case of a 50-year-old male who developed severe hypoglycaemia after Roux-en-Y gastric bypass (RYGB), illustrating the role of selective arterial calcium stimulation test (SACST) in the diagnosis and management of hypoglycemia. Our patient presented with recurrent hypoglycaemia one to two hours after meals, which started 15 years post RYGB performed for morbid obesity with hypertension, impaired glucose tolerance, NAFLD and ischemic heart disease. The hypoglycaemia events were severe and frequent, with glucose levels reaching 39 mg/dl (2.2 mmol/l) associated with altered level of consciousness. During these events, patient had high insulin (1086 pmol/l), proinsulin (26.2 pmol/l), and C-peptide (6.08 nmol/l) levels, normal levels of beta-hydroxybutyric acid, with negative sulfonylurea screen, negative insulin antibodies and normal IGF2 levels, all suggestive of endogenous hyperinsulinemia. The patient failed to have hypoglycaemia during a mixed meal test and a 72- hour fast. He had normal thyroid, kidney and adrenal function tests. Imaging and functional studies of the pancreas and abdomen were negative; these included abdominal computed tomography, abdominal magnetic resonance imaging and Gallium Dotatate PET CT. In addition, endoscopic ultrasound (EUS) was performed and did not show any pancreatic masses. Acarbose was initiated with dietary modification which included a low carbohydrate and high protein diet, however, hypoglycaemia episodes persisted. He was then started on daily octreotide injections and nifedipine. The hypoglycaemia episodes became less severe and less frequent subsequently. To further investigate the source of endogenous hyperinsulinemia in our patient, a selective arterial calcium stimulation test (SACST) was performed in order to differentiate between insulinoma (uni or multifocal) and non-insulinoma pancreatogenous hyperinsulinemia. This showed two to threefold increase in insulin levels post arterial calcium stimulation in all pancreatic regions and no tumor blush was observed. Therefore, the test did not localize a focal region of the pancreas that is responsible for excess insulin secretion and that would be amenable to surgery. Lastly, he was not a candidate for gastrojejunostomy stoma reduction/plication as there was evidence of Roux-en-Y anatomy with a micro pouch on upper endoscopy. Reversal of the bypass was also discussed but not pursued given patient's morbid obesity and overall poor health condition. The decision was to continue with medical and dietary therapies for non-insulinoma pancreategenous hyperinsulinemia. Our case illustrates the importance of SACST in the evaluation of endogenous hyperinsulinemic hypoglycaemia with negative localization studies. In this case, it spared the patient from undergoing an additional highly morbid surgery (pancreatectomy).

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EP402

Estimation of reproductive state in women with DM1

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Introduction

Past years with increasing of duration of life, improving of treatment and increasing of life longevity and new knowledges about Diabetes Mellitus pathogenesis and treatment rise interest to reproduction in these women, especially with type 1 DM. Well known, that late puberty, abnormal menstrual cycle, pregnancy and childbirth pathology, infertility. The aim of our study was investigate the functional state of reproductive system in woman with DM1.

Material and Methods

72 control female patients with type 1 diabetes and 40 healthy women were examined. The age of the examined patients ranged from 11 to 28. In all female patients blood plasma FSG, LG, Estrogen, Progesterone, Testosterone level were determined by the enzyme immunoassay method, uterine and ovarian Ultrasound were performed.

Results

In patients with DM1 blood plasma level of Estrogen were decreased in 60% of them, Progesterone - in 24%, Testosterone - in 45%, whereas FSG and LG levels were increased and suggested about hypergonadal hypogonadism in women with DM1. Anamnesis data shown among women with DM1 about 44% had amenorrhea, 16% had infertility, 11% had stillbirth, and 9% had premature birth. On ultrasound examination of the uterus and ovaries in women with DM1 shown that 20% had uterine hypoplasia and was in line with blood hormones level.

Conclusion

In observed woman with DM1 according to anamnestic data shown abnormalities in functional state of reproductive system such as amenorrhea (44%), infertility (16%), stillbirth (11%), premature birth (9%), which accompanied with decreasing of peripheral sex hormones level and increasing of pituitary hormones and uterine hypoplasia (20%) on ultrasound suggested about hypergonadal hypogonadism.

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EP403

The association between vitamin D3 deficiency and acute kidney injury in COVID-19 patients

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Introduction

Vitamin D deficiency is a common clinical finding in the general population and hospitalized patients, including patients in the intensive care unit(ICU). Acute kidney injury (AKI) occurs in more than 50% in ICU admitted patients.

Objectives

Due to the fact that there are few studies about AKI in COVID-19 patients, we investigated the relationship between vitamin D3 deficiency and the occurrence of AKI in COVID-19 patients.

Patients and Methods

This cross-sectional study was conducted on 69 COVID-19 patients who were hospitalized in the ward for 12 months. Their serum vitamin D3 levels were measured in the first 24 hours of hospitalization in the ward. Patients were divided into three groups based on the serum level of vitamin D3: >50 ng/ml: normal, 20-50 ng/ml: insufficient, <20 ng/ml: deficiency. The patients were studied until the occurrence of acute renal injury or the occurrence of death.

Results

Out of 69 hospitalized patients in the ward with COVID-19, there were 39 patients in group vitamin D3 <20 ng/ml, 21 patients in group vitamin D3 20-50 ng/ml and 9 patients in group vitamin D3 >50 ng/ml. The frequencies of AKI in group vitamin D3 <20 ng/ml, 20-50 n/ml, and >50 ng/ml were 46%, 28%, and 23%, respectively. Significant relationship was observed between AKI and our study groups (*P*-value $=$ 0.011). Furthermore, there was a significant association between our study groups and mortality (*P*-value $=0.014$), ICU admission (*P*-value $=0.041$) and hospital length of stay (*P*-value $=0.017$). In another division in patients with different levels of vitamin D3 in the presence or absence of AKI, there was a significant association between group of patients with vitamin D3 <20 ng/ml in presence of AKI and mortality ($P=0.042$), ICU admission (*P*-value $=0.024$) and hospital length of stay (*P*-value $=$ 0.027).

Conclusion

Our study showed significant association between vitamin D deficiency and AKI in ICU-admitted COVID-19 patients. Moreover, there was relationship between vitamin D deficiency and mortality, ICU admission and hospital length of stay. These results suggest the correction of vitamin D deficiency may be beneficial to reduce AKI in patient with COVID-19.

Keywords: AKI, Vitamin D deficiency, COVID-19

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EP404

Effects of Metabolic Syndrome on Cardiovascular Outcomes of Psoriatic Patients With Coronary Artery Disease

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Background
Psoriasis is associated with a heightened prevalence of cardiovascular risk factors, including metabolic syndrome (MetS). As so far, it is not clear whether MetS will cause differences on clinical outcomes of psoriatic patients who have already suffered from coronary artery disease.
Methods
We conducted a retrospective cohort study to determine the effects of MetS in psoriatic patients with coronary artery disease. Comparisons were made between patients with and without MetS. The Cox regression analysis and Kaplan-Meier survival analysis were used to evaluate the association between variables.
Results
Of the 307 participants, 94 met criteria (30.6%) for MetS. Individuals with MetS were more common in females ($P<0.001$). The levels of platelet counts and hsCRP were higher in the MetS group ($P=0.038$ and 0.005, respectively). After the mean follow-up of 35.32 ± 18.61 months, major adverse cardiovascular events (MACEs) and non-fatal myocardial infarction were more prone to occur in MetS group than Non-MetS group (33.3% vs 20.6%, $P=0.02$; 26.4% vs 15.7%, $P=0.032$, respectively). Kaplan-Meier estimates showed the same trend. The COX regression analysis showed that MetS [hazard ratio (HR) = 1.738, 95% confidence interval (95%CI): 1.045–2.891, $P=0.033$] and left ventricular ejection fraction (HR = 0.968, 95%CI: 0.945–0.991, $P=0.006$) were associated with an increased risk of MACEs.
Conclusion
In psoriatic patients with coronary artery disease, MetS was more common in females and it independently predicted MACEs. In addition, left ventricular ejection fraction was associated with an increased risk of MACEs. To reduce the cardiovascular disease risk associated with MetS, it is necessary to increase awareness of the condition.

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EP405

Adherence to lipid lowering treatment in type 2 diabetics with dyslipidemia

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Introduction
Dyslipidemia is highly prevalent in patients with type 2 diabetes, which increases the risk of cardiovascular disease in these patients. Lipid-lowering treatment has demonstrated beneficial effects in the primary and secondary prevention of cardiovascular events.
Objective
Evaluate the therapeutic compliance of dyslipidemia treatment in type 2 diabetic patients and identify the factors limiting the follow-up of the therapeutic prescription in them.
Materials and Methods
It was a cross-sectional study, including 60 patients with type 2 diabetes hospitalized in the department C of the National Institute of Nutrition of Tunis for 3 months (October-December 2022).
Results
The mean age was 51.67 ± 12.5 years. The sex ratio was 0.3. The mean duration of diabetes was 11.1 ± 6.1 years. One third of patients were treated with insulin (30.4%). Cardiovascular risk was moderate, high, and very high in 17.9%, 50% and 32.1% of patients, respectively. Among all participants, mixed- dyslipidemia was the most prevalent (52.2%), followed by hypercholesterolemia (27.6%) while hypertriglyceridemia was identified in 20.2% of patients. Dyslipidemia was treated with atorvastatin in 82.1% of cases. In primary prevention, no patient reached the therapeutic goals, whereas in secondary prevention, the objectives were reached in only 13.2% of cases. Only 46.4% of patients reported following the clinical and biological monitoring rhythm after starting a statin treatment. More than half of the patients (56.5%) reported stopping treatment on their own. The main reasons for non-adherence to statin therapy were high cost, unavailability of treatment, side effects, and poly-medication reported in 46.2%, 23.1%, 7.7%, and 23.1% of cases, respectively. However, two thirds of patients receiving statins were not informed about their effectiveness in cardiovascular protection.
Conclusion
Non-adherence to lipid-lowering treatment in type 2 diabetic patients is a limiting factor in therapeutic efficacy. Strengthening therapeutic education for these patients would be essential to improve adherence to medical prescriptions and prevent cardiovascular events in this at-risk population.

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Combination of mutations in the HNF1A and ABCC8 genes: Clinical polymorphism in members of the same family

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Mutations in HNF1A gene underlie the development of maturity onset diabetes of the young type 3 (MODY3). Mutations in ABCC8 gene are the cause of neonatal DM and the rare MODY12, which is clinically similar to MODY3. In these forms of MODY, there is a high sensitivity to sulfonylurea, but over time, patients may need insulin therapy.
Patient A, 17 y.o. He was born to woman with gestational DM. At the age of 12.5, fasting hyperglycemia of 13 mmol/l was detected. Insulin therapy was not prescribed due to the parents refusal. At the 14.5 y.o, since his mother was diagnosed with MODY3, a pathogenic variant p.R54X in HNF1A was detected, a MODY3 was diagnosed. At the age of 15, he was hospitalized with hyperglycemia 13.8 mmol/l. HbA1c - 9.8%. Long-acting insulin was assigned. Subsequently, the patient used insulin irregularly and consumed large amounts of fast carbohydrates. His maximum HbAc1 was 20.5%. At 17 y.o, he was admitted to hospital: glycemia was 18.6 mmol/l, HbAc1 - 12.6%, islet antibodies were negative. Intensified insulin therapy (0.9 units/kg/day) led to the normalization of glycemia. Specific diabetic complications were not detected. In addition to the variant in the HNF1A, a p.R521X variant was found in the ABCC8. After 3 months, the boy was successfully transferred to glibenclamide 7.5 mg/day.
Patient L, 37 y.o, proband's mother. At the age of 20, gestational DM was diagnosed: fasting glycemia was 6-9 mmol/l, she refused insulin therapy. At the 32 y.o, an examination for cholelithiasis revealed hyperglycemia, the variant p.R54 X in the HNF1A was detected. To date, she has not received hypoglycemic therapy, followed a carbohydrate-restricted diet. At the last examination at the age of 37, HbAc1 was 6.7%, a variant of p.R521X was found in the ABCC8 as in the son.
Patient S, 8 y.o, proband's sister. HbAc1 – 5.4%, fasting glycemia – 4.7 mmol/l. There are variants of p.R54X in the HNF1A and p.R521X in the ABCC8.
Conclusion
MODY associated with variants in the HNF1A and ABCC8 is characterized by a different degree of carbohydrate metabolism disorders, depending on the location of mutation in gene and its severity. We have presented a description of clinical polymorphism in members of family with a combination of identical mutations in the two MODY genes. The more severe disease in proband, apparently, is due to the low compliance. Normoglycemia in sister may be due to age, which requires further dynamic observation.

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EP407

The influence of the metabolic profile on the manifestations of diabetic neurogenic bladder

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Objective
To determine the influence of metabolic disturbances associated with diabetes mellitus (DM) on the clinical manifestations of the diabetic neurogenic bladder (DNB).
Patients and Methods
Analytical cross-sectional study comparing two groups of patients suffering from DM: G1 ($n=159$) with manifestations of DNB versus G2 ($n=41$) without signs of DNB.

Results
G2 patients were younger than G1 patients (58±12 years vs 59.7±10.3; $P=0.36$) with a female predominance (63.4% vs 52%; $P=0.16$). The duration of diabetes was significantly longer in G1 (11.9 vs 7.7 years; $P=0.03$). A glycemic imbalance was statistically more pronounced in G1 (88% vs 61%; $P=0.000$). Patients in G1 were more likely to have high blood pressure (53.8% vs 30%) and dyslipidemia (59.7% vs 47.5%) without statistical significance. The mean BMI was significantly higher in G1 (29.2±5.5 vs 26.4±4.2 kg/m^2; $P=0.03$). The mean waist circumference was also greater in G1 (103.5 vs 95.7 cm; $P=0.01$). The prevalence of obesity was higher among G1 patients (34% vs 14.6%; $P=0.016$). Although more prominent in G1, the metabolic syndrome did not appear to significantly influence the clinical manifestations of DNB (65.8% vs 34.2%; $P=0.07$).
Discussion
Certain metabolic disturbances, notably android obesity, seem to be a factor aggravating the manifestations of DNB. Through chronic inflammation and alteration of para-sympathetic neurons, obesity-induced insulin resistance disturbs bladder muscle function. Thus, several studies highlight the interest in weight loss as a therapeutic target to improve the symptoms of DNB in obese patients with DM.
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EP408

« Echocardiography indicators after endovascular revascularization in patients with type 2 diabetes mellitus and chronic heart failure»
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Aim
To study the parameters of heart Doppler before endovascular revascularization in patients with type 2 diabetes mellitus and without it in patients with coronary artery disease.
Research Material
60 patients (prospectively) with CHF were examinedafter endovascular revascularizationin the period of 2021 at the Center of Surgery named after acad. V.V. Vakhidov.All observed patients were divided into 2 groups: 1 gr. – 35 patients with DM2 with CHF and undergoing CABG. 2 gr. – 25 patients with CHF without DM2 who underwent CABG. The control group consisted of 20 patients with type 2 diabetes without CHF. To characterize the examined patients were used: general clinical, biochemical and instrumental examinations.
Material and Methods
general clinical, biochemical (bilirubin, direct, indirect, lipid spectrum, ALT, AST, coagulogram, blood sugar, glycated hemoglobin, urea, creatinine, GFR, galectin-3, insulin, renin, aldosterone in the blood) and instrumental: ECG, Echo-ECG, cardiac angiography, Dopplerography of the main vessels of the heart and legs, ultrasound of internal organs, fundus.
Results
We analyzed 60 patients with type 2 diabetes mellitus complicated by coronary artery disease and chronic heart failure. Of these, 19 women, 41 men. Biochemical blood tests showed that the average values of the lipid spectrum were significantly increased in all patients of groups 1 and 2, compared with the control group ($P<0.05$).The next stage of our research was to study the relationship between various parameters and LV ejection fraction on Echo-ECG by groups. In patients of group 1, Echo-ECG showedrevealed left ventricular dysfunction and cardiomyopathy in 100% of cases, while in patients of group 2 thesechanges were detected in 17% of cases ($P<0.05$). In patients of group 1, hemodynamic parameters of the heart were significantly lower than in patients of group 2.
Conclusions
It was found that in patients of groups 1 and 2, no significant differences in mean age, BMI, glycemia, renin values, insulin, HOMA index were found depending on the EF values. At the same time, the significance of differences was revealed only for aldosterone and galectin-3; these values significantly increased as EF decreased in patients of group 1. ($P<0.05$).
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EP409

"Features of Doppler ultrasound of the heart and kidneys in patients with type 2 diabetes mellitus with cardio-renal syndrome"
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Purpose of the Study
To study the relationship between the renal perfusion index and systolic heart function in type 4 cardiorenal syndrome in patients with type 2 diabetes mellitus"
Material and Research Methods
The study, which was performed from January to May 2022, included 48 patients with type 2 diabetes mellitus and stage 1-3 CKD. (16 F, 32 M, age 50±17 years, BMI 27.02±3.44 kg/m^2) according to the study protocol. Hypertensive nephropathy (HT-CKD) addressed 12 patients. None of the patients included in the study had heart failure. The control group consisted of 20 patients with DM2 without CHF and without CKD. The study used clinical and biochemical research methods (glycemia, glycated hemoglobin, IRI, C-peptide, ALT, AST, bilirubin, urea, creatinine, PTI, hormonal studies (renin, angiotensin, aldosterone) as well as instrumental methods of examination - ultrasound internal organs,ultrasonography with an assessment of the overall intensity of cortical perfusion of the kidneys and the renal perfusion index (RPI),ECG, Echo-ECG, indicators of the quality of life of patients (questionnaire), as well as statistical methods.
Research Results
Analyzing the data of dopplerography of the heart and kidneys, we present for the first time the effect of systolic heart function on RI in patients with type 2 diabetes with CKD. This allows with the probability of early non-invasive detection of cardiac systolic pathology during ultrasound of the kidneys, when high-quality ultrasound examination of the structures of the heart is impossible (lack of technique, emphysema, obesity). Finally, it is likely that RI assessment may be useful for early detection of CRS associated with reduced cardiac output [14]. However, the applicability of RI for diagnosing early anomalies of the cardio-renal axis requires further study.
Conclusions
1) In the group of patients with DM 2 and CKD stages 1-3 without CHF, we detected Echo-ECG changes according to the type of LV diastolic dysfunction of 1-2 degrees with a tendency to increase the mean pressure in the pulmonary artery. 2) RI can be used as an independent marker for predicting the outcomes of CKD in type 2 DM.
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Etiological profile and outcomes of acute pancreatitis in patients with type 1 diabetes
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Objective
To describe the etiological profile the outcomes of acute pancreatitis (AP) in patients with type 1 diabetes (T1DM).
Patients and Methods
A retrospective descriptive study of 10 T1DM patients who presented at least one episode of AP during their follow-up.
Results
The mean age at diagnosis of T1DM was 19.7±9.3 years, with a female predominance (60%). T1DM was frequently inaugurated by a cardinal syndrome (50%) or spontaneous diabetic ketoacidosis (DKA) (20%). In 10% of patients, T1DM was diagnosed at the time of AP. The episode of AP occurred at a mean age of 26.9±14.9 years. In 57.1% of the cases, the AP wasclassified as stage E. Stages A, B, or C were less commonly reported with a frequency of 14.3%, each. The identified etiologies of AP were autoimmune (20%) or major hypertriglyceridemia (10%). In 70% of the cases, the mechanism of AP remained undetermined. Despite a favorable outcome after the first episode, recurrence of AP is still frequent in T1DM with a rate of 16.7%. Discussion: The pathophysiological mechanism of AP in patients with T1DM remains poorly understood. The consequences of AP on pancreatic tissue previously weakened by autoimmune destruction related to T1DM would be more prominent compared to control subjects. Thus, our work highlights an increased incidence of stage E with more frequent recurrence in this population. Further studies with a large number of subjects are needed to find more precise explanations.

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EP411

Glycosylated haemoglobin levels in new and known diabetes patients with hyperglycaemic ketoacidosis

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Background/Aims
Ketosis in patients with known Type 2 diabetes mellitus is overlooked due to atypical symptoms. Type 2 diabetes (DT2) is characterized by a longer period of asymptomatic hyperglycaemia than Type 1 diabetes(DT1). The objective of this study was to compare glycosylated haemoglobin (HbA1c) levels in ketoacidosis (DKA) occurring in known and newly diagnosed diabetes.
Methods
This is a retrospective cross-sectional descriptive study concerning all patients hospitalized in the Endocrinology Department for DKA between November 2021 and January 2022. HbA1c levels were determined on ADAMS ® Arkray at presentation. The data were analyzed using SPSS 26.
Results
There were 14 known DT1 or DT2 patients and 6 newly diagnosed diabetes. The mean age was 24±8.30 years The mean HbA1c of all admissions was 12.03±2.96% ($n=20$) . The mean HbA1c in known DT1 or DT2 and newly diagnosed diabetes patients were similarly high 11.6±3.2% and 13.6±1.6% (P0.15) respectively. The averages of HbA1c above 8% were statistically similar in the both groups of patients (93.3% in known DT1 or DT2 vs 100% in newly diagnosed diabetes patients.
Conclusions
DKA is associated with markedly elevated HbA1c levels in known DT1 or DT2 and new onset diabetes.

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EP412

An inaugural diabetic ketoacidosis revealed by odontogenic facial cellulitis

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Introduction
Odontogenic facial cellulitis (OFC) is a soft cellulo fatty tissue infection of lesser resistance in different spaces, delimited by the musculoaponeurotic insertions on the maxillary and mandibular bone cortices. when patients have underlying diseases such as diabetes mellitus (DM) or cancer, compromised immune systems may lead to the opportunistic progression of seemingly minor infections. We report the case of a patient who presented an inaugural diabetic ketoacidosis (DKA) revealed by OFC.
Case Report
A 40- year-old female patient with a passive smoking history, presented to the emergency department for consciousness disorders, interview with the family reveals the notion of a toothache 2 weeks before complicated by jugal pain and fever. The physical assessment had revealed a tchycardia of 122 bpm, 100/63 mmhg blood pressure, high respiratory rate 29 cpm and 39.2 °C of temperature. The face was swollen and erythematous with trismus. A facial CTscan was performed which showed collection of the left masseter muscle, hypodense, peripherally enhanced with air bubbles measuring $16^{\times}35.5^{\times}33.5$ mm with thickening of the left jugal subcutaneous soft tissue. In the side the biological assessment was in favor of an elevated plasma glucose level of 4.2 g/l, metabolic acidosis and urine ketones. C-reactive protein level was at 291 mg/l with white blood cell count 25910 per mm^3. The diagnosis of OFC with an inaugural diabetic ketoacidosis was retained. After stabilization, the management consisted of surgical drainage of the abscess with antibiotic therapy guided by the result of the antibiogram of the pus sample, in addition to insulin therapy and rehydration.
Discussion and Conclusion
OFC is a rare but serious infection which can engage the vital prognosis by its encephalic complication like the thrombophlebitis of the cavernous sinus and cervical like the collections or even mediastinitis especially when it occurs in an immunocompromised state such as diabetes. The diagnosis must be suspected in front of any inflammatory facial pain or swelling on a precarious dental ground. The corner-stone of treatment is based on broad-spectrum antibiotics with surgical draining in suppurative phase in parallel with the management of diabetic decompensation.
Keywords: inaugural DKA-facial-odontogenic cellulitis.
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Risk factors for lower limb amputation in patients with diabetes

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Introduction
The diabetic foot is a frequent complication that can be life-threatening for the diabetic patient. The risk of amputation is multiplied by 40 in the diabetic patient compared to the non-diabetic population. Our aims were to determine the prevalence of foot amputation in patients hospitalized for poorly controlled diabetes, and to determine the risk factors associated with amputation.
Method
This is a cross-sectional analytical study, including type 2 diabetic patients hospitalized at the National Institute of Nutrition in Tunis during the year 2021.
Results
Our study included 209 patients with type 2 diabetes, of which 121 are female and 88 are male. The mean age was 51±18 years. The average duration of diabetes was 11.6±8.8 years, and more than half (55.5%) of the patients had diabetes older than 10 years. Among the study population, 42 patients were active smokers. Alcohol consumption was noted in 6.2%. Hypertension, dyslipidemia, and hypothroidism were present in 50.2%, 59.8%, 8.6% of the patients respectively. Moreover, obesity was noted in 28.7% of patients. The average glycated hemoglobin was 10.6±2%. Nine patients had a history of lower limb amputation due to diabetic foot complications. The antecedent of amputation was significantly higher in men ($P=0.005$), and increases significantly with the duration of diabetes ($P=0.01$). However, there was no association with smoking, alcohol consumption and amputation. Lower limb amputation for diabetic foot was significantly associated with diabetic nephropathy ($P=0.012$) cerebral vascular accident ($P=0.029$), and autonomic neuropathy ($P=0.019$). Nevertheless, it was not associated with coronary artery disease and diabetic retinopathy.
Conclusion
In our study we found that the risk of amputation increases with the presence of other degenerative complications of diabetes. This emphasizes the importance of regular follow-up to detect and prevent the development of these complications.

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Diabetes and cardiovascular risks (about 557 cases)

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Introduction
Alone or associated with other vascular risk factors, diabetes is responsible for heavy morbidity and mortality all over the world.
Objective of the Study
To stratify diabetic patients according to cardiovascular risk anddetermine the elements that increase this risk.
Materials and Methods
Retrospective, cross-sectional and descriptive study of patients followed in the endocrinology, diabetology and metabolic disease department of CHU IBN Rochd in Casablanca, The cardiovascular risk was assessed according to the

recommendations of theEuropean Society of Cardiology (ESC), European Association for the Study of Diabetes (EASD) on diabetes and prediabete.
Results
Our study involved 557 diabetic patients, with an average age of 51.19 years, with a female predominance in 64% of cases. Among our patients; 79% had type 2 diabetes and 21% had type 1 diabetes. Mean HbA1c was 10.3%. For associated cardiovascular risk factors; 42% were hypertensive, 29% dyslipidemic, 16% were smokers and 30% had obesity. Regarding the degenerative complications of diabetes, 16% of cases already presented a cardiovascular event and 34% of patients had microangiopathy (10% nephropathy and 24% diabetic retinopathy). In our series, 40% were at very high risk, 39% at high risk and 21% had a moderate cardiovascular risk. In patients who were at very high cardiovascular risk, this was mainly linked to organ damage and the age of diabetes or the fact that diabetes was associated with another cardiovascular risk factor.
Conclusion
Our study has shown that the cardiovascular risk in diabetic patients is strongly linked to degenerative complications, hence the interest of their early detection and the use of the choice of anti-diabetics which have demonstrated better cardiovascular and renal prevention. .

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EP415

Low-density lipoprotein cholesterol target achievement in patients with diabetes: A Tunisian study

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Background and Aim
Diabetes is often associated with other cardiovascular (CV) risk factors wich elevates morbi-mortality in these patients. Primary and secondary CV prevention depends on the control of CV risk factor including low- density lipoprotein cholesterol (LDL-C) level. The aim of this study was to assess the CV risk level of diabetic patients and to determine the rate of lipid targets achievement.
Methods
It was a descriptive cross-sectional study including 122 type 2 diabetes patients. All patients had mixed dyslipidemia treated by statins.CV risk level and LDL-c goal achievement were assessed according to European Society of Cardiology updated guidelines in 2021. New is the introduction of a stepwise approach to intensify preventive treatments.
Results
The mean age was 58.56 ± 9.05 years with a female predominance (56.5%). Mean diabetes duration was 13 ± 7.44 years, mean glycated hemoglobin was 9.9% $\pm$ 1.74, 20.4% of patients used oral glucose-lowering drugs (OGLDs) only,and 79.6% used OGLDs plus insulin .Only 12.5% used insulin analogs. Microvscular complications were present in 52.1% of patients. Meam Body Mass Index was 29.53 ± 8.07 kg/m^2 ,59% of patients had high blood pressure and 22.66% were tabacco users. Mean dose of Atorvastatine was 40 mg, prescribed as secondary prevention in 13.7% of cases. According to new guidelines, 23.3% and 76.7% were considered at very high and high CV risk, respectively. Step1 LDL-c goals were achieved in 65.1% of cases while step 2 LDL-c goals were achieved in 32.1% of patients according to their CV risk level. Patients at high and very high CV risk achieved LDL-c goal level in 27.5% and 4.6% of cases respectively. Non-achievement of LDL-c goals was due to non-availibility of treatment in 40% of cases and poorly adapted dosage in 36.6% of cases.
Conclusions
Most of patients didn't achieve recommended goals likely due to non avaibility of treatment and therapeutic inertia.The cost of treatment could explain these results as this later is a fundamental criterion in countries with low financial resources as Ezetimibe and PCSK-9 inhibitors are not available or available at high cost.

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EP416

Smoking during pregnancy is not a risk factor for gestational diabetes mellitus: A systematic review and meta-analysis

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Background
While the association between cigarette smoking and type 2 diabetes is established, the impact of smoking on developing gestational diabetes mellitus (GDM) remains controversial.
Aim
To investigate whether maternal cigarette smoking during pregnancy is a risk factor for developing GDM.
Methods
MEDLINE, Scopus, CENTRAL and Google Scholar databases were searched from inception to December 2022 to identify eligible original articles. A systematic review and meta-analysis (weighted data, random-effects model) were performed. The primary outcome was the development of GDM in pregnant women. The results were expressed as odds ratios (OR) with 95% confidence interval (CI) (Inverse Variance method). Subgroup analysis was planned according to the maternal smoking status and GDM diagnostic criteria. Statistical heterogeneity was checked with the Chi-squared (Chi^2) test and the I^2 index was used to quantify it. The studies were evaluated for publication bias. A sensitivity analysis was performed to assess the effect of each study.
Results
Thirty-five studies, including 23,849,696 pregnant women, met the inclusion criteria. The pooled OR of cigarette smoking during pregnancy compared with non-smoking (never smokers and former smokers) was 1.06 (95% CI 0.95-1.19), $P=0.30$; $I^2=90\%$; $Chi^2=344$; $df=34$; $P<0.001$. Subgroup analysis was performed according to the Carpenter-Coustan GDM diagnostic criteria, due to the high heterogeneity among the other applied methods. The pooled OR for GDM for the studies that applied the Carpenter-Coustan criteria was 1.19 (95% CI 0.95-1.49), $P=0.12$; $I^2=63\%$; $Chi^2=27$; $df=10$; $P<0.002$. Further subgroup analysis according to maternal smoking status was not performed due to missing data.
Conclusions
There is no evidence to support an association between maternal cigarette smoking during pregnancy and the risk for GDM. Universally accepted diagnostic criteria for GDM must be adopted to reduce heterogeneity and clarify the association between smoking and GDM.

Keywords: gestational diabetes mellitus; GDM; cigarette smoking; tobacco; pregnancy; perinatal

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EP417

Main risk factors for Hyperglycemia in Pregnant Bulgarian Women

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The conducted national screening of Bulgarian pregnant women showed a frequency of Hyperglycemia among them of 14.4%. It is known that a number of factors have a significant impact on this disorder. The aim: to assess risk factors for the development of Hyperglycemia in pregnant women in Bulgaria.
Material
We screened 547 pregnant women, mean age 30.49 ± 5.12 years, divided into two groups: up to 24 gestational week –g.w. (n-386, 70.6%) and after 24 g.w. (n-161, 29.4%).
Methods
BMI before pregnancy and the current one at the time of the study were calculated. A two-hour, 75 g oral glucose tolerance test (OGTT) was performed. Plasma glucose was quantitatively determined using enzymatic reference method with hexokinase (Roche reagent) in the Central laboratory on the day of the blood sampling. The results were in mmol/l. The statistical analysis was performed using SPSS 13.0 for Windows.

Results
The screened pregnant women had Hyperglycemia in fasting state or during OGTT in 7.5% in group up to 24 g.w. vs 31% in group after 24 g.w, $P<0.01$. The age of the group of pregnant women with Hyperglycemia (n-79) vs the others with Normoglycemia (n-468) was significantly higher - 32.18 ± 5.26 years v.s. 30.21 ± 5.05 years, $P<0.005$. The women with a higher BMI before and during pregnancy are significantly at risk of developing glucose disorders during pregnancy, $P<0.0001$. Family history of diabetes occurred in 29.1% (n-23/79) of the pregnant women with Hyperglycemia, vs 13.5% (n-63/468) of those with Normoglycemia, $P<0.001$. There was a significant difference between the incidence of Hyperglycemia in pregnant women with previous GDM compared with those without - 3/79 (3.8%) vs 3/468 (0.6%), $P<0.04$.
Conclusion
Considering the main risk factors for Hyperglycemia during pregnancy, identified in the screening - advanced maternal age, obesity, family history of diabetes, and previous GDM, a verbal screening would be very helpful and would direct us to screen each pregnant woman with any of these risk factors.
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EP418

Evaluation of diabetes-associated antibodies in patients With newly diagnosed type 1 diabetes mellitus

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Introduction
The presence of diabetes-associated antibodies is an indicator of β-cell destruction. Our goal was to find out the prevalence of autoantibodies associated with the new onset of type 1 diabetes mellitus (DM1) without family history.
Subjects and Methods
22 patients (10 women and 12 men) with newly diagnosed DM1 no family history were examined. Average age of patients was 31.7 ± 7.3 y.o., experience of DM1 was 2.3 ± 0.8 months. All the patients underwent the determination of autoAbs, such as glutamic acid decarboxylase (GAD-Ab), islet antigen-2 (IA2-Ab), and islet cell cytoplasmic (ICA-Ab), zinc transporter 8 (ZnT8-Ab). The determination of the level of antibodies was carried out by the method of quantitative enzyme immunoassay using the analyzer Freedom Evo (Tecan).
Results
GAD-Ab were found in 90% of the examinees. IA2-Ab were observed in 36%. ZnT8-Ab were detected in 14 patients (63.6%). Auto-Antibodies were more frequently observed in combination than alone. 13 patients (59%) had ZnT8-Ab and GAD-Ab. IA2-Ab, GAD-Ab and ZnT8-Ab were detected in 5 patients (22.7%). ICA-Ab were not detected.
Conclusion
The antibodies that are most frequently observed in newly diagnosed DM1 are GAD-Ab, IA2-Ab and ZnT8-Ab. Along with GAD-Ab antibodies, it is possible to determine ZnT8-Ab and IA2-Ab antibodies, since ZnT8-Ab and IA2-Ab are detected in 63.6% and 36% of patients, respectively. We have not identified ICA-Ab, which confirm the usefulness of this investigation.
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EP419

Degenerative profile in diabetic patients and their glycemic control: Epidemiology in morrocan diabetics

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Background and Aims
The objective of our study is to evaluate the degenerative profile in diabetic patients and their glycemic control
Materials and Methods
This analytical cross-sectional study for analytical purposes was conducted during the period from January 2022 to January 2023, within the department of endocrinology and metabolic diseases of the Military Hospital of Instruction Mohamed V of Rabat.
Results
215 patients were included, all with type 2 diabetes, whose mean age was 59.3 +/- 8.59 years. 54.9% (118) were male with a sex ratio (M/W) of 1.21. HbA1c was less than 7.5% in 41.4% (89) of the patients, and the median age of diabetes was 10 [6,14.5] years. Regarding the antidiabetic treatment; 33% (71) of our patients were under oral treatment containing a hypoglycemic sulfonamide, 26% (56) were under oral treatment without sulfonamide, 30.7% (66) were under basal-bolus insulin therapy, and 10.2% (22) were under bed-time. The degenerative complications of diabetes were present in 47% of cases, distributed as follows: 34% (75) of the patients had diabetic retinopathy, 18.6% (40) had diabetic nephropathy, 6.5% (14) had ischemic heart disease, 1% (2) had ischemic stroke and 2.3% (5) had diabetic neuropathy. In multivariate analysis, and adjusting for age, sex, duration of diabetes and glycemic control, the duration of diabetes (OR: 1.26 IC95% [1.09-1.45]) is a risk factor for microangiopathy while intensification of treatment with insulin therapy is a protective factor (OR:0.056 IC95%[0.2-0.8]), for macroangiopathy: male sex (OR:1.3 IC95%[1.2-0.0025]) glycemic imbalance and insulin therapy are risk factors ($P<0.001$ OR > 1).
Discussion
The degenerative complications are the gravity of diabetes mellitus, Their frequency increases with that of diabetes; according to the IDF (International Diabetes Federation): DR is present in 35% of diabetic patients, and remains among the first causes of blindness, the same result has been reported in our study 34%. The IDF also reports a rate of 36% of diabetic patients suffering from ND, a rate that is much higher than that found in our study. Regarding macroangiopathic complications; coronary artery disease was present in 6.5% of our patients, the IDF reported a much higher figure between 12 and 31%, while only 1% of our patients reported a history of stroke.
Conclusion
In spite of the efforts made by the learned societies, diabetes remains a frequent and serious disease by its evolution towards complications difficult to avoid, and involving a major social and personal handicap.
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EP420

Auditing inpatient diabetes care in Our Lady of Lourdes Hospital, Drogheda, Ireland

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Optimal in-patient glycaemic control improves morbidity and mortality in in-patients with diabetes[1]. The National Inpatient Diabetes Audit (NaDIA) is an annual snapshot audit of diabetes inpatient care in England and in Wales. We performed a similar audit in Our Lady of Lourdes Hospital, Drogheda (OLOLHD, 363 in-patient beds) on 26/01/2022 and 08/10/2020. Data from all adult in-patients with diabetes were gathered using a standard proforma. Data from the OLOLHD 2022 cohort were compared to those from either the OLOLHD 2020 cohort or the 2019 NaDIA annual report using Fisher's exact test or the independent-samples *t*-test. The prevalence of in-patient diabetes in OLOLHD was similar in both years (12.9% ($n=47$) vs 13.2% ($n=48$), $p>0.99$). Neither age (71.1 ± 16.4 vs 75.4 ± 12.8 years, $P=0.159$) nor length of stay (15.7 ± 28.4 vs 13.6 ± 16.0 days, $P=0.664$) differed between the two time-points audited. Feet were examined in 4.2% of the 2022 cohort ($n=2$), 6.4% of the 2020 cohort ($n=3$, $P=0.677$) and 33.6% of the NaDIA 2019 cohort ($n=5.201$, $P<0.001$). A glycaemia management error occurred in 18.8% of the 2022 sample ($n=9$), 8.5% of the 2020 sample ($n=4$, $P=0.232$) and 30% of the NaDIA 2019 sample ($n=4.643$, $P=0.113$). A member of the diabetes team reviewed 31.3% of OLOLHD diabetes in-patients in 2022 ($n=15$) and 74.7% of UK diabetes in-patients in 2019 ($n=11.563$, $P<0.001$). Despite less in-patient diabetes resource being available in OLOLHD, there was a trend towards less glycaemia management errors here. More effort needs to be put into making foot examination routine.
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EP421

The impact smoking on the course of type 2 diabetes mellitus. Case study

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Introduction
We already know that smoking is one of the causes of type 2 diabetes. Cigarette smoking increases the risk for type 2 diabetes incidence and is an independent risk factor for type 2 diabetes. Nicotine in tobacco is responsible for the association between cigarette smoking and development of diabete.
Aim
The purpose of this study was to evaluate the impact of smoking on the course of type 2 diabete.
Material and Methods
A total of 191 patients were included in the study, divided into four groups based on whether they smoked or not and on medication. Group 1: smoking ($n=39$), Group 2: non-smoking ($n=153$), Group 3: treatment of diabetes drugs ($n=77$), group 4: treatment of insulin ($n=114$).
Results
The mean age of 62.23 ± 10.85 years (43-82 years) with a sex ratio (M/F) of 0.94. The majority were 114 patient (59.6%) type 2 diabetics treatment of insulin and 77 patient (40.3%) treatment of diabetes drugs. The mean age of diabetes was 9.74 ± 4.23 year (0:30). The mean HbA1C was $8.35\pm6.59\%$ (4.8-13.3%). Obesity was present in 56.4% of patients. The incidence of hyperuricemia was 21.8%. In ours study were noted smoking in 39 patient (20.4%) of cases of wich 28 patient (71.7%) were men and 11 patient (28.2%) were women. 27 patient (69.2%) in treatment of diabetes insulin and 12 patient (30.7%) patient in treatment of diabetes drugs. The mean HbA1C of smoking patients was $8.55\pm4.04\%$ (4.6-12.2%). Diabetes was found to be balanced in 18 patient (46.1%) smoking of wich 12 patient (66.6%) in treatment of diabetes insulin with HbA1C $6.86\pm3.70\%$ (4.6-7.5%) and 6 patient (33.3%) smoking in treatment of diabetes drugs with HbA1C $6.94\pm3.72\%$ (5.7-7.5%). The mean HbA1C it was not comparable between the two smoking groups.
Conclusion
Smoking increases not only the risk for type 2 diabetes mellitus but there is also has an impact on its progress. Our study showed that individuals with type 2 diabetes mellitus and smokers had a poor course of diabetes compared to non-smoking individuals with type 2 diabetes mellitus and smoking individuals treated with insulin had better progress than those treated with drugs.
Keywords: Smoking, ,non-smoking, insulin, drugs.
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EP422

CoMICs (Concise Medical Information Cines) videos on diabetes mellitus and polycystic ovary syndrome have better quality, content, and reliability compared to videos from other sources

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Introduction
It is important to ensure the information shared on social media is up to date to current clinical practice, reliable and appropriate to the target audience. YouTube is the most popular social media platform for video-based medical information worldwide. You and Your Hormones is a UK-based website endorsed by Society for Endocrinology hosting videos on various medical conditions aimed at the public. CoMICs (Concise Medical Information Cines) are short videos providing bite-sized information on a variety of topics using illustrations and infographics. We compared the quality of diabetes and PCOS videos between CoMICs, YouTube and You and Your Hormones.
Method
A search using the terms "Diabetes" or "PCOS" was conducted on YouTube on 26th October 2022. The search was limited to those videos with content in English and a duration of less than 10 minutes. After excluding videos with no audio, in non-English language or duration longer than 10 minutes, the top 50 most popular videos in the category of diabetes and in PCOS were included in this study. All videos related to diabetes or PCOS on the CoMICs website were also included in the study. All 124 included videos were evaluated for content, quality, and reliability using three video analysis tools: Quality Criteria for Consumer Health Information (DISCERN), Global Quantitative Strategies (GQS), and Journal of the American Medical Association (JAMA) benchmark criteria. The average score from two independent reviewers was obtained for all videos. Grouped scores in the three scoring systems were compared between YouTube videos and CoMICs.
Results
CoMICs videos had overall higher mean DISCERN scores compared to YouTube videos across both diabetes (CoMICs vs YouTube vs Your and Your Hormones: 2.4 ± 0.6 vs 1.6 ± 0.4 vs 1.5 ± 0) and PCOS (2.9 ± 0.64 vs 1.9 ± 0.5 vs 1.5 ± 0). CoMICs videos had the highest DISCERN score for reliability (25.4 ± 2.6 vs 19.1 ± 3.9 vs 19 ± 0). The median (IQR) GQS scores between the three groups were similar at 3 (2-4), 3 (2-4) and 3.5 (2.75-4). No video met all the JAMA criteria. JAMA scores for authorship across the three groups were 100% vs 32.3% vs 50%. Overall, CoMICs were of higher quality compared to YouTube and You and Your Hormones.
Conclusion
CoMICs videos have a higher level of accuracy and reliability compared to YouTube and You and Your Hormones on diabetes and PCOS, making them a reliable source of medical information for both patients and healthcare professionals.
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EP423

Plasma Renin activity in patients with Diabetes Mellitus

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Introduction
Renin angiotensin system play a crucial role in the development of Diabetes Mellitus and its complications. According many studies, plasma renin level increased at the DM. However, mechanisms of its elevation is not clear yet. The aim of our study was compare plasma renin level in DM1 and DM2 patients and its relationship with glycemic control.
Material and Methods
In 44 people with DM1 and 85 with DM2 whose admitted into Hospital of the Republican Specialised Scientific Practical Medical Centre Endocrinology were collected clinical and anamnestic data, hemodynamic status, blood glycemia, HbA1c, and blood plasma renin activity were measured using immunoassay.
Results
Patients average age were significantly differ by type 19.0 ± 2.33 and 58.17 ± 1.17 y.o. DM duration were 2.51 ± 0.94 and 8.74 ± 0.93 years in DM1 and DM2 groups respectively. HbA1c level were $10.7\pm0.38\%$ in DM1 and $8.86\pm0.27\%$ in DM2 patients. Plasma renin activity were significantly higher than in healthy people in both group and was in 1.2 times higher in DM2 group. Interestingly, Plasma renin activity shown correlation with age, urine protein, also with FIB4 score in patients with DM1 but no any correlation found in DM2 group. Thus, results suggested about different mechanisms of elevation of plasma renin activity in DM1 and DM2.
Conclusion
Plasma renin activity significantly increased in both DM1 and DM2 groups, and suggested about high activity of RAAS. Plasma renin activity shown correlation with age, urine protein level in DM1 group, but not in DM2 and proposed about different mechanisms of its elevation depending of type.
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EP424

The dynamics of growth in the frequency of Charcot foot in the Republic of Uzbekistan for the period 2012 - 2021 years

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Aim
To study the frequency of Charcot foot in the Republic Uzbeistan during 2012-2021 years.
Material and Methods
Reports of regional endocrinological dispensaries of 13 regions of the country and the Republic of Karakalpakstan for the studied period were used. In total, in 2012, 2648 patients with a foot Charcot were registered. All patients during the observation period were subjected to general clinical, biochemical (control of glycemia, HbA1C ,et al), instrumental (ECG, X -ray of the foot, examination of the oculist other) research method.
Results
During the period 2012-2021, the frequency of Charcot foot in country increased by 4.3 times. So, if in 2012 2648 patients with a foot of Charcot consisted in the country, then in 2021 their number reached 11560.Among the leading regions was the Ferghana region: in 2012, 1430 patients were registered there, and in 2021 already 2145. It should be noted that in 2012 year, 116,517 patients with DM 2 were registered in the Republic Uzbekistan, and in 2021 year-291 567 patients. Such an increase in the number of patients with a foot of Charcot foot can be explained both by an increase in the splash of DM 2 and an improvement in the detection of its complications.
Conlusion
During the period 2012-2021, the frequency of Charcot foot in the Republic of Uzbeistan increased by 4.3 times. Such an increase in the number of patients with a foot of Charcot foot can be explained both by an increase in the splash of DM 2 and an improvement in the detection of its complications

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EP425

Association of Latent Autoimmune Diabetes of the Adults with other systemic and organ-specific autoimmune diseases

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Introduction
Latent autoimmune diabetes of the adults (LADA) is a heterogeneous type of diabetes sharing clinical characteristics of type 2 DM and serum markers of pancreatic autoimmunity detected in type 1 DM. It accounts for 2-12% of all patients with diabetes. The aim of our study is to identify the association between LADA and other systemic or organ-specific autoimmune diseases.
Materials and Methods
We conducted an observational study in the outpatient clinic of autoimmune endocrinopathies of the Department of Pathophysiology at Laikon University Hospital. All patients were positive for GAD antibodies. They were also evaluated for TPOAbs, TGAbs, APCA, ANA and clinical information for other systemic autoimmune diseases were obtained from their medical record. Demographic data and clinical characteristics regarding the age of LADA onset, duration of LADA, time span not requiring insulin treatment, BMI, metabolic syndrome and chronic related diabetic complications were also collected. Laboratory tests for FPG, basal c-peptide and insulin, HbA1c were performed.
Results
A total of 24 patients were analyzed. Mean age was 55.5 ± 13.4 years, 91.7% of them were females and 33.3% were smokers. Mean BMI was 22.9 ± 3.8 kg/m^2, HbA1c at diagnosis was 8.65 ± 1.7%, mean c-peptide $= 0.49 \pm 0.59$ ng/ml and mean anti-GAD titer $= 80.3 \pm 7.8$ IU/ml. 22.7% had metabolic syndrome and 17.39% presented with chronic LADA related complications. Autoimmune gastritis with positive APCA antibodies was present in 31.25% of the patients and thyroid autoimmunity with positive TgAbs and/or TPOAbs in 50%. Moreover, ANA were positive in 41.6% of our patients. There is a statistical significance among LADA and thyroid autoimmunity, autoimmune gastritis and other autoimmunities ($P = 0.0000073$, $P = 0.0000074$ and $P = 0.00049$, respectively).
Conclusion
In our study we demonstrated a statistical significant association between LADA and thyroid autoimmunities, autoimmune gastritis and other systemic or organ specific autoimmune diseases.

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EP426

Maternal weight status and gestational diabetes

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Introduction
Maternal overweight is a major risk of gestational diabetes that can impair glycemic control. The objective of our study was to assess the impact of maternal weight status on glycemic control and pregnancy outcomes in patients followed for gestational diabetes.
Methods
Our work is a retrospective study, including 182 patients with gestational diabetes followed in the Endocrinology-Diabetology department between January 2016 and January 2022.
Results
The study included 182 patients with an average age of 32 years. The mean term at first visit was 21 weeks of amenorrhea (AS). The mean pregestational BMI was 29 kg/m^2. The average intake of weight was $+6$, 7 kg. all patients ($n = 7$) with a BMI < 18.5 kg/m^2), were on a hygiene-dietetery diet, with a weight gain of $+0.37$ kg/SA. Those with a BMI between 18.5-24.9 kg/m^2, 85.71% ($n = 60$) were on a hygiene-dietetery diet, with a weight gain of $+0.39$ kg/SA, 14.29% ($n = 10$) on insulin. BMI between 25-29.9 kg/m^2 with a weight gain of $+$ 0.4 kg/SA, 94.51% ($n = 86$) observed insulin therapy, 5.49%($n = 5$) on a hygiene-dietetery diet. Patients with a BMI > 30 kg/m2 with a weight gain of $+$ 0.42 kg/SA were all on insulin. However, weight gain was significantly greater in patients treated with insulin than in those treated with a hygiene-dietetery diet ($P = 0.06$).
Discussion
Maternal hyperglycemia during GDM was related to pregestational weight status and weight gain appeared to be a factor associated with insulin therapy. Hence the interest of raising awareness among patients from the prenatal consultation.

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EP427

Autoantibody-negative insulin-dependent diabetes mellitus after COVID 19: Case report

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Introduction
The COVID pandemic was a challenge in terms of physiopathology and therapeutics. Diabetics represent more than 40% of patients hospitalized for COVID. There was many new cases of diabetes declared during or after a COVID. The purpose of this report is to raise the link between Sars-Cov-2 infection and the appearance of glycemic disorders and new cases of diabetes.
Case Presentation 1
A 28-years-old man who had a serious COVID-19 a month ago, treated in intensive care with corticosteroid therapy. He had no diabetic family history. His BMI was in the normal range. He presented classic type 1 diabetes symptoms with ketoacidosis. His glycated hemoglobin was at 8.8%. His serum anti-GAD and anti IA2 antibodies were negative. He received insulin therapy.
Case Presentation 2
A 34-year-old overweight woman who had a mild Sars-cov-2 infection treated at home; she has an obvious autoimmunity history. No diabetic family history. She presented few months later severe symptoms of hyperglycemia and ketosis, her glycated hemoglobin was at 12.9%. She had negative antibodies. She was on insulin.
Discussion
The relationship between diabetes and COVID-19 is bidirectional. Diabetes exposes to a higher risk of severe COVID and more mortality. Furthermore, COVID exposes to more metabolic complications and possible diabetes new cases. This issue have been raised after an increase in new cases of diabetes after the pandemic stated in multiple studies. Several cases of post COVID diabetes with negative antibodies have been reported in the literature. Most of them were patients between 26 and 50 years-old, who all had a type 1 diabetes clinical presentation with a post-COVID delay ranging from one week to 3 months. They all had negative antibodies. Some of the cases reported were no longer on insulin, which the authors attributed to a possible transient

pancreatic dysfunction. The mechanisms of the pancreatic dysfunction suggested were: A direct effect of the virus on the pancreatic beta-cell; the triggering of the immune reaction leading to type 1 diabetes; the systemic inflammatory response or the cytokine storm; the effect of prescribed corticosteroid therapy and the effect of the lock-down independently of the viral infection itself. A study confirmed the presence of Sars-cov-2 in beta cells of patients who died of COVID.
Conclusion
Current data have confirmed the hyperglycemic power of Sars-cov-2 virus, through a complex and multifactorial mechanism, but do not confirm its direct role in the appearance of a new diabetes type.

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EP428

Evaluation of physical activity and sleep patterns in patients with type 2 diabetes during the month of Ramadan

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Introduction
Fasting during Ramadan very often requires a change in lifestyle for patients and adaptation is not easy in individuals with type 2 diabetes (T2D). Physical activity, sleep duration and sleep time are subject to change during Ramadan, due to changes in the number and times of meals.
Study Objectives
This study aims to assess the physical activity and sleep patterns of T2DM patients during Ramadan.
Material and Methods
We assessed physical activity using the IPAQ questionnaire and the impact on sleep patterns (quality and quantity) during the month of Ramadan using the PSQI form and a sleep quality rating scale ranging from 1 to 10. Data analysis was done with SPSS software version 25.
Results
Fifty patients were enrolled in our study, all T2DM, 80% of whom were on ODA during the month of Ramadan over a period of 29 days. The average age was 60.4 years, our study included 34 women for 16 men with a sex ratio M/F of 0.47. By making an average distribution over 24 hours, the average duration of sports activity is 47 minutes ($\pm$7 minutes), that of night prayers is 1 h20 mn ($\pm$ 10 minutes), the average duration of household chores is 3 hours ($\pm$23 minutes), daily shopping takes an average of 1 hour. There is a significant reduction in the total number of hours of sleep and The average total sleep duration is 4 hours 35 min ($\pm$28 min). Only 15 patients (30%) took an average nap of 52 minutes. Nighttime sleep quality was observed to be low in this period, with 38 patients or 76% reporting early morning awakening and 22 patients (44%) reporting sleep-onset insomnia. hours of nighttime sleep during the period of Ramadan with a shift in the sleep slice. The overall assessment of sleep quality (night and nap) remains fairly good at 20% ($n=10$); Somewhat poor in 70% ($n=35$); very bad in either 10% of patients or $n=5$.
Conclusions
Our study shows a high prevalence of low physical activity among people with T2DM during Ramadan, and short sleep durations during Ramadan compared to the period outside Ramadan. A larger study is needed in the future covering before, during and after Ramadan to assess the impact of lifestyle changes related to fasting during Ramadan in type 2 diabetics.

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EP429

Dimensions of sexuality among women with type 2 diabetes mellitus: A comparative study

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Introduction
Sexuality can include several dimensions such as thoughts, fantasies, desires, beliefs... But these can be influenced by biological, psychological, socio-economic factors or somatic pathologies, such as diabetes. The aim of our study was to evaluate the sexuality of women with type 2 diabetes mellitus and its different dimensions, as well as the predictive factors of female sexual dysfunction (FSD) among this population.
Methods
This is a comparative study of 30 women with type 2 diabetes mellitus (G1) compared to a control group of 30 women (G2) collected from the department of the National Institute of Nutrition. Sexual function was assessed using the "Female Sexual Function Index (FSFI)" survey. A score of less than 26.55 characterizes FSD. We compared the dimensions of sexuality according to the FSFI survey for the 2 groups.
Results
The mean age of the patients was 42.97$\pm$6.6 years. A high level of education was noted in 30% of women with diabetes and 45% of controls. The mean total FSFI score was 25.53$\pm$6.11 for G1 and 29.75$\pm$4.19 for G2. FSD was diagnosed in 53% of G1 vs 17% of G2. All dimensions of sexuality were affected according to the scores of desire, arousal, lubrication, orgasm as well as satisfaction. The mean score of all dimensions was lower for the G1 compared to G2. Sexual desire is strongly affected by the duration of diabetes ($P=0.016$) as well as parity ($P=0.02$). The advanced age of the patients is correlated with a low level of sexual arousal ($P=0.04$). 40% of women who had FSD wanted to consult a sexologist. Higher level of education was strongly correlated with this request ($P=0.03$).
Conclusion
These results justify the imperative of systematic screening and appropriate management of FSD in order to improve quality of life. The evaluation of sexuality is therefore necessary for an early treatment of these disorders in order to avoid conflicts and marital disagreements, sources of stress and therapeutic resistance.

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EP430

YouTube Videos adressing diabetes: is popularity correlated with quality?

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Introduction
Nowadays, social media has become a valuable source of health-related information which can have an important impact on people's behaviors and decisions regarding their diseases. To improve management of diabetes, patients often seek health information in social media platforms, including Youtube. We aim in this review to analyse factors associated with the popularity of videos found on YouTube that adress diabetes management.
Methods
A YouTube query using the search terms "diabetes treatment" in arab language was performed at the date of January 17th 2023.The most viewed 50 videos which first appeared in the search results were included in the analysis. The reliability of the videos was determined using the modified DISCERN criteria, and the quality with the Global Quality Score. Visual quality was also assessed. Popularity was determined by views number, likes and comments.
Results
The video quality was assessed by the Global Quality Standard and the mean score was 1.78 $\pm$0.61. The reliability of the videos was determined using the modified DISCERN criteria was at 0.86$\pm$0.64. Popularity didn't correlate neither with quality nor reliability. Graphic and audio quality didn't correlate with popularity. Average likes numbers was 48153 for videos sharing incorrect and misleading informations, and 14560 for those with only correct content ($P=$ 0.0001). Average commentes number was 1597 for videos sharing incorrect content, and 843 for those containing correct informations ($P=0.04$). The percentage of videos containing false and misleading informations was 63% of the total.
Conclusion
The most popular videos often content unreliable, incorrect, even dangerous content. This may have harmful consequences for the diabetes community. More studies are needed to analyse the reasons explaining this paradoxical phenomenon.

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EP431

Relationship between Blood Glucose and Urine Glucose Levels in Type 2 Diabetes Mellitus Patients on sodium-glucose co-transporter-2 inhibitor Therapy

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We evaluated the relationship between blood glucose and urine glucose levels in type 2 diabetes (T2D) patients who had reached steady state upon taking a sodium-glucose co-transporter-2 inhibitor (SGLT-2 inhibitor). Ten patients with T2D taking Luseogliflozin 2.5 mg for more than 2 weeks were hospitalized for diabetes treatment. During hospitalization, the patients used a continuous glucose monitor (CGM) [iPro2] for 6 days (CGM attachment: day 1) while continuing Luseogliflozin 2.5 mg intake. All other antidiabetic treatments were adjusted to improve glycemic variability. From day 2 to day 5, starting from 9 AM, we obtained four consecutive 24-hour mean blood glucose levels (24-h MGL) and 24-hour urine glucose levels (24-h UGL), respectively. "24-h MGL and 24 h-UGL during the same period" (paired MUGL) were compared. We arranged paired MUGL in descending order of 24-h MGL. Then, consecutive 20 paired MUGLs were selected while shifting selection start one by one. Estimated glomerular filtration rate (eGFR) was measured once during hospitalization. For each selected group, we used multivariate linear regression analysis to predict the 24-h UGL from the 24-h MGL and eGFR, where we commonly applied eGFR as a pair for the four paired MUGLs per each patient. One paired MUGL was excluded from the analysis due to inaccurate urine glucose measurement. The arranged paired MUGL were numbered from 1 to 39 and consecutive 20 paired MUGLs were selected 20 times (from "1–20" to "20–39": 20 groups). 24-h MGL positively correlated with 24-h UGL ($r=0.81$; $n=39$). For the results analyzed using multivariate linear regression analysis in each group, standard partial regression coefficient (β) for eGFR, β for 24-h MGL, p for eGFR, p for 24-h MGL, adjusted-R2 for a regression formula (RF), and p for RF correlated with mean of 24-h MGL in each group ($r=$–0.61, –0.76, 0.72, 0.62, –0.62, and 0.62, respectively; $n=20$). Under steady state for SGLT-2 inhibitor in T2D, decreased 24-h MGL may be associated with decreased 24-h UGL. Increased 24-h MGL could lead to a reduced ability of predicting 24-h UGL using both 24-h MGL and eGFR.

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EP432

Whey Protein in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Background
Type 2 Diabetes Mellitus is the more prevalent type, caused by a combination of insulin resistance and inadequate insulin response to hyperglycemia1. Aside from pharmacologic interventions, medical nutrition therapy is an integral part of the management of patients with Type 2 Diabetes Mellitus. Whey protein, which is one of the best protein sources, has been investigated for its applicability in improving glycemic control in patients with Type 2 Diabetes Mellitus. This systematic review and meta-analysis was conducted to measure the magnitude of the effect of whey protein on glycemic control in type 2 diabetes mellitus. The aim of this review is to evaluate the efficacy and safety of whey protein in patients with type 2 diabetes mellitus.
Methods
A systematic electronic search for studies in the PubMed and Cochrane Collaboration database was done. Included in this review were randomized controlled trials of whey protein enrolling patients with type 2 diabetes mellitus. Three reviewers independently searched, assessed and extracted data from the individual studies.
Results
A systematic literature search on online databases such as Cochrane Central Registry, PubMed and Herdin Plus was conducted in April to September 2021 to identify eligible studies. The search yielded 21 randomized controlled trials after removing duplicates. Only 5 articles were included after reviewing the full text which met the criteria for selection.
Conclusion
Whey protein supplementation significantly reduced fasting blood glucose. However, it did not reduce post-prandial blood glucose, HbA1c level and weight when compared with placebo. There has been a considerate heterogeneity across all studies for which may have contributed/confounded with its effects. A larger sample size and better inclusion and a more specific study may be included in the future reviews.

Keywords: "whey protein", "diabetes", "nutrition", "fasting blood sugar", "postprandial glucose", "HbA1c", "weight reduction"
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EP433

Can exenatide, an antidiabetic drug, cause chronic pancreatitis? A case presentation

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Introduction
Pancreatitis is one of the serious side effects of glucagon-like peptide-1 receptor analog exenatide, which is an incretin hormone with anti-glycemic effects secreted from the intestine and is used for treating type 2 diabetes.
Case
A 60-year-old female patient with type 2 diabetes mellitus for 11 years had been using exenatide for 6 years (no history of acute pancreatitis) along with insulin glargine and metformin. She was admitted to the emergency department with complaints of nausea, vomiting, and abdominal pain radiating to the back for the last 3 days. The patient's laboratory results are shown in Table 1. Possible factors, other than the ones associated with exenatide, (alcohol, hypertriglyceridemia, infections, and other drugs) were excluded. Contrast-enhanced computed tomography revealed multiple calcifications in the pancreatic parenchyma and irregular dilatation of the main pancreatic duct that was 17 mm in width at its widest point. Additionally, 7 mm calculus was found in the main pancreatic duct at the level of the papillary opening. These findings were indicative of chronic pancreatitis. In addition to these data, endoscopic retrograde cholangiopancreatography (ERCP) was performed. ERCP showed dilatations and stenosis along the entire pancreatic duct and fibrotic bands in the parenchyma, which indicated toward chronic pancreatitis. Therefore, exenatide was removed from the patient's treatment regimen, and she was discharged and prescribed metformin, dapagliflozin, gliclazide MR, and glargine.
Discussion
It has been reported that the risk of pancreatitis in patients with diabetes is 3–4 times higher than in the non-diabetic population. The risk of pancreatitis in general patient population using exenatide is 0.34–0.44 times higher than other patients. This risk is 2.83 times higher in people with diabetes. As the risk of pancreatitis is increased in patients with diabetes mellitus using exenatide, it might be beneficial to prescribe alternative drugs to these patients.

Table 1 Demographic and laboratory data in the diabetic patient

Age (year)	60
BMI (kg/m^2)	29.4
Amylase (U/l)	46 (28-100)
Lipase (U/l)	26 (7-60)
T.Cholesterol (mg/dl)	150 (120-200)
LDL (mg/dl)	112 (0-130)
Triglyceride (mg/dl)	87 (40-180)
HbA1c (%)	9.6 (4.6-6)
Creatinine (mg/dl)	0.5 (0.6-1.2)
AST (UL)	17 (5-40)
ALT (UL)	8 (5-40)
ALP (U/l)	113 (30-120)
GGT (U/l)	14 (0-55)
T. Bilirubin (mg/dl)	0.3 (0-1.1)
D. Bilirubin (mg/dl)	0.1 (0-0.35)
Hb (g/dl)	12.9 (11.1-17.1)
Plt (×109/l)	438 (140-360)
WBC (×109/l)	11.74 (3.8-8.6)
Albumin (g/dl)	4.07 (3.5-5.3)
Ca (mg/dl)	8.62 (8.5-10.8)

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EP434

Effect of semaglutide on weight, hba1c and liver enzymes in type 2 diabetes patients

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Introduction
Type 2 diabetes, obesity and fatty liver disase are the most common comorbidities at the orgin of metabolic syndrome. Treatment of these conditions overlaps significantly. The most recent innovation in the armamentarium of pharmacotherapy of type 2 diabetes is Glp 1 agonist, More recent research on the effect of GLP-1 receptor agonist on weight loss, metabolic parameters and fatty liver disease are promising. The weight reduction offered by GLP-1 agonist treatment has significant impact on the progression of fatty liver. Semaglutide, a weekly GLP 1 agonist, is used to treat type 2 diabetes patient and more recently approved for the treatment of obesity in patient without type 2 diabetes.Newsome et al, have shown that ALT normalized in 25-48% subjects treated with semaglutide (1).
Rational
The rational of this study is to assess the improvement of hba1c, weight reduction and improvement in AST and ALT in type 2 diabetes patients treated with semaglutide.
Methods
50 patients attending Endocrinology Clinic in Mediclinic Parkview Hospital and Mediclini Dubai mall and started on Semaglutide were followed. Hba1c, weight and AST ALT levels were recorded before and 6months and 12 months after starting semaglutide.
Results
Our sample included 50 treated subjects (43 male (86%), 7 female). While the medication did not show a significant reduction in ALT and AST levels in 6 months, semaglutide showed a significant reduction in weight in 6 months. 82% of the sample had an average of 5% percentage change reduction in weight from baseline to 12 months, with all 7 women having reduced on 11% average and men with 4% percentage reduction in weight. Semaglutide also had a significant relation with HbA1c, showing reduction at 6 months (-0.15 percentage points, $P<0.001$) as well as in 12 months (-0.14 percentage points, $P<0.001$).
Discussion
Our study have shown two established benefits of semaglutide, a reduction of hba1c and reduction of body weight. However it did not show a signficiant improvement in AST and ALT, one possible explanation is that the sample of patients did not have established fatty liver disease at baseline, they were also not followed for a long enough period of time to establish a significant relationship.

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EP435

A case of euglycemic ketoacidosis under iSGLT2 and a review of literature about predictive factors

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Introduction
SGLT2 (sodium-glucose cotransporter 2) inhibitors are a molecule more and more used in type 2 diabetes. However, it can cause a metabolic decompensation in some cases. Euglycemic ketoacidosis may be atypical, misplacing and delaying the diagnosis. We investigated the precipitating factors of this metabolic complication in our case study and in the literature.
Presentation of the Case
We report the case of a normal BMI (19 kg/m^2) ,66-year-old woman with incidentally discovered diabetes for 3 years, switched from dual oral antidiabetics to insulin analogues (basal-plus regimen (0.48 IU/kg/24 h)) a year before her hospitalization. Since the patient did not accept the multiple insulin injections, she was put on hypocaloric diet and changed to an insulin bedtime regimen with the addition of Dapagliflozin (10 mg/d). A few days later, she went to the emergency room with asthenia, epigastralgia, vomiting and dyspnea. At the workup, venous glucose was 10 mmol/l. On urine dipstick, glucosuria was two crosses and acetonuria was four crosses. On arterial blood gas, the patient presented a severe metabolic acidosis (PH=7.08, bicarbonates at 8) with hypocapnia (PCO2 at 27). The diagnosis of severe euglycemic ketoacidosis was retained and the patient was transferred to the intensive care unit where she received hydration, insulin therapy with an electric syringe pump with adapted potassium supplementation and discontinuation of oral antidiabetics. The ketoacidosis was resolved after three days. The insulin regimen was re intensified.
Discussion
Euglycemic ketoacidosis under iSGLT2 can be explained by several mechanisms, mainly the alteration of the insulin/ glucagon ratio. iSGLT2 increases glucagon production by directly stimulating pancreatic alpha cells but also in response to the decrease in blood glucose. Glucagon increases the activity of CPT-I (carnitine palmitoyl transferase-I) inducing the overproduction of ketone bodies[1]. Conditions such as relative insulin deficiency, low body mass index with reduced glycogen stores and a low carbohydrate diet are then predictive factors of ketoacidosis under iSGLT2[1]. Other precipitating factors may include pancreatic damage and alcoholism. In our case, the reduction of insulin doses, the hypocaloric diet and the low BMI could be the incriminating factors.
Conclusion
Euglycemic ketoacidosis under iSGLT2 is a rare and serious entity which can be overlooked in the face of normal blood glucose. A clinical attention should be carried to predictive factors.
Reference
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EP436

Audit on the effect of oral Semaglutide on HbA1c and Weight reduction in type 2 diabetes

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Background
Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) which is widely used for the management of type 2 diabetes as well as for the obesity treatment. Evidence suggest that the level of HbA1c reduction and weight loss with oral semaglutide were similar to those of the subcutaneous formulation[1]. However, oral formulation not only improves the patient's compliance to treatment but also makes it a favourable option for those who are reluctant to use an injectable agent. The aim of this audit is to evaluate the effect of oral Semaglutide on mean reduction of HbA1c and weight following mean duration of treatment of 6 months.
Materials and Methods
A comprehensive retrospective review of patient's clinical and laboratory database was conducted for 36 patients (22 males / 14 females, mean age 58±20 years, duration of diabetes 20 years or less) in our region in County Durham Darlington, United Kingdom during the period between September 2020 - March 2022. The starting dose of oral Semaglutide was 3mg for the first month, 7 mg during the second month and then increased to 14 mg from third month onwards. The effect of this drug on mean reduction in HbA1c and weight was measured following mean duration of 6 months of treatment.
Results
At baseline, mean HbA1c was 75.3±19 mmol/mol and mean weight was 97.4±27 kg among the audited 36 patients. The mean duration of treatment was 6.2 months (95% CI=3, 14 months). Following 6.2 months of treatment, mean HbA1c was 67.7±17 mmol/mol and mean weight was 94.9±26 kg. Hence, mean HbA1c reduction was 7.5 mmol/mol (95% CI=-44, 41 mmol/mol) and mean weight reduction was 2.53 kg (95% CI=-9.2, 3.14 kg). The p-value was 0.01.
Conclusion
To conclude, we can say that, oral Semaglutide is an effective pharmacological agent in reducing both HbA1c and weight. However, our observations need to be confirmed in larger cohorts and for extended period of treatment.
Reference
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EP437

Real-world effectiveness analysis of oral versus subcutaneous semaglutide in patients with type 2 diabetes mellitus

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Background and Objective
Semaglutide, a glucagon-like peptide 1 (GLP1a) receptor agonist, reduces the risk of major adverse cardiovascular events in patients with type 2 diabetes mellitus (DM2). An oral version of semaglutide is now available, and patients may prefer it to the subcutaneous form. Our objective was to compare the effectiveness and safety of both formulations in real life.
Methods
Retrospective real-world efficacy analysis including aGLP1-naïve adults with T2DM who were started on oral or subcutaneous semaglutide add-on to T2DM treatment during the year 2022. The primary outcome was change in HbA1c. Secondary outcomes were changes in weight and lipid profile, occurrence of gastrointestinal side effects (GSEs), and discontinuations. Linear mixed models were used to estimate changes in HbA1c, weight, and BMI, and logistic regression was used to analyze GSEs and discontinuations.
Results
136 patients were included, 82 in the subcutaneous semaglutide group and 54 in the oral semaglutide group. Mean age was 60 years (SD 1.5) and HbA1c 8.2% (SD 0.2). At 24 weeks, the mean reductions in HbA1c were: -1.2% (SD 0.2) with subcutaneous semaglutide and -1.3% (SD 0.2) for oral semaglutide (p n.s). The mean changes in body weight from baseline to week 24 were: -5.5 kg (SE 2.3) for subcutaneous semaglutide and -6.9 kg (SD 2.4) for oral semaglutide, (p n.s). There were no differences in the lipid profile. Some type of adverse event occurred in 41 patients in the subcutaneous semaglutide group (50%) and in 21 patients in the oral semaglutide group (39%), mostly mild gastrointestinal effects. There were 11 withdrawals from treatment in the subcutaneous semaglutide group (13.4%) and 5 in the oral semaglutide group (9.2%).
Conclusion
Semaglutide, in its two presentations (subcutaneous and oral) are effective in the treatment of patients with DM2. There were no differences in HbA1c, weight, or lipid profile, or in the appearance of adverse effects or dropouts.

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EP438

The influence of the endocrinologist in the management of type 2 diabetes

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Introduction
In Spain, the specialist in endocrinology and nutrition is the reference in the care of patients with diabetes mellitus. In the year 2022, access to these specialists has been facilitated in the south of Gran Canaria. The aim of the study is to determine how this has influenced the management of type 2 diabetes (T2D).
Methods
We included those patients with T2D assessed by the Endocrinology service in 2022 in which two analyses were performed 6 months apart. Patients diagnosed with T2D in 2022 or who had been assessed by an endocrinologist after July 2021 were excluded. The change in glycosylated haemoglobin (HbA1c) and LDLc was assessed in all patients and by subgroups. The change in anti-diabetic and lipid-lowering treatment was studied. In addition, we analysed the influence on metabolic control of the introduction of basal insulin, iSGLT2, aGLP1 and assessment by the hospital dietician team.
Results
A total of 77 patients were included, 58.41% were male. The mean duration of diabetes was 12.28 years. 76.62% were in primary prevention. The change in HbA1c, expressed in%, with basal insulin initiation (4 patients), iSGLT2 (16 patients), aGLP1 (16 patients) and assessment by dietician (13 patients) was 10.45 ± 1.67 vs 7.33 ± 1.12 ($P = 0.125$), 7.981 ± 1.44 vs 6.694 ± 0.73 ($P = 0.0004$), 8.33 ± 1.71 vs 6.687 ± 0.80 ($P = 0.0002$) and 7.523 ± 1.84 vs 6.646 ± 0.83 ($P = 0.415$), respectively.
Conclusion
Patients with T2D managed by endocrinologists have improved metabolic and lipid profile control. There has been a marked increase in the use of iSGLT2, aGLP1 and statins, as recommended in disease management guidelines. The introduction of iSGLT2 and aGLP1 achieved a statistically significant decrease in HbA1c.

Table 1 Change in HbA1c, expressed as%, and in LDL-C, expressed as mg/dl

	Patients	Initial	6 months	*P*
HbA1c		7.36±1.37	6.67±0.73	<0.001
HbA1c >7	34	8.52±1.28	7.04±0.75	<0.0001
HbA1c > 8	18	9.45±1.11	7.30±0.80	<0.0001
LDLc		95.7±42.60	75.5±33.00	<0.001
LDLc > 70	51	117.6±31.90	85.5±33.45	<0.0001
LDLc > 100	34	135.2±23.57	90.8±38.02	<0.0001

Table 2 Use of drugs, expressed as a percentage of patients

Drug	Initial	6 months	Change
Basal insulin	18.2	23.4	+5.2
Bolus Insulin	7.8	6.5	-1.3
Metformin	76.6	77.9	+1.3
iDPP4	32.5	24.7	-7.8
aGLP1	13.0	32.5	+19.5
iSGLT2	42.9	62.3	+19.5
Sulfonylurea	10.4	7.8	-2.6
Glinides	2.6	3.9	+1.3
Pioglitazone	1.3	3.9	+2.6
Statin	64.9	88.3	+23.4
Ezetimibe	13.0	22.1	+9

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EP439

Effect of Liraglutide on glycemic control in type 2 diabetic patients

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Introduction
Liraglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA), approved for management of type 2 diabetes (T2D).
Aim
The aim of our study is to evaluate the effectiveness of Liraglutide in controlling blood glucose levels over a period of 6 to 12 months in Tunisian type 2 diabetic patients.
Methods
We conducted a prospective descriptive study at the endocrinology-nutrition department of the military hospital of Tunis, including 22 patients with T2D who were not treated with GLP-1 RAs. Liraglutide 1.2 mg was administered subcutaneously once daily. Fasting glycemia and glycated hemoglobin were checked before and 6 to 12 months after starting treatment. Clinical and paraclinical data were collected from medical records.
Results
Our population included 8 men and 14 women. The mean age was 53.8 ± 9 years old. The mean duration of diabetes was 11.2 ± 6.9 years. Our patients had a mean weight of 109 ± 19.2 kg and a mean BMI of 39.4 ± 7 kg/m^2. Hypertension, dyslipidemia and coronary artery disease were found in respectively 15, 16 and seven patients. Nineteen patients were treated with metformin, 15 patients with dipeptidyl peptidase inhibitors, 16 patients with sulphonylureas and five patients with insulin. The mean HbA1c was 10 ± 11.3% before starting Liraglutide and 8.4 ± 1.8% after 6 to 12 months of treatment ($P = 0.004$). The mean fasting blood glucose was 2.1 ± 0.5 g/l before starting Liraglutide and 1.7 ± 0.5 g/l after 6 to 12 months of treatment ($P = 0.049$). Glycemic control remained stable in three patients, worsened in four patients, and improved in 15 patients. Ten patients achieved therapeutic targets of HbA1c. Among those treated with sulphonylureas, the dose was reduced in 10 patients. Among those treated with insulin, the dose was reduced in four patients.
Conclusion
Our study shows the effectiveness of Liraglutide, used in combination with other hypoglycemic agents, in reducing HbA1c and glycemia in patients with T2D.

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EP440

Glycaemic control parameters in patients with diabetes mellitus secondary to exocrine pancreas diseases using flash glucose monitoring

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Introduction
Diabetes mellitus secondary to exocrine pancreas diseases (pancreatogenic DM) has an unknown incidence and is considered underdiagnosed. Our objective was to evaluate the glycemic control parameters in patients with pancreatogenic DM who started Flash glucose monitoring (FGM).
Methods
Prospective, observational study in a Spanish hospital. Patients with pancreatogenic DM who started FGM from January 2021 to August 2022 were recruited. Patient data collected included demographic, clinical, anthropometric variables, and the etiology, years of evolution, and treatment of DM. Additionally, following blood glucose control variables from the Abbott FreeStyle Libre were recorded for the first 14-days: glucose management indicator (GMI), coefficient of variation (CV), percentage of time in range (TIR) (70-180 mg/dl), in hypoglycemia (<70 mg/dl), in hyperglycemia (>180 mg/dl) and hypoglycemic events.
Results
20 patients were included. 60% were men. Median age was 63 [IQR 57-76] years and evolution of DM was 6.5 [IQR 3.0-11.7] years. 55% were secondary to pancreatectomy (30% total, 25% partial), 25% chronic pancreatitis, 15% cystic fibrosis, and 5% hemochromatosis. Regarding of chronic complications, 15% had cardiovascular disease, and 35% microvascular complications (25% nephropathy, 15% retinopathy, 5% nephropathy). Median weight was 66.1 [IQR 61.1-71.7] kg and BMI 25.4 [IQR 22.8-27.5] kg/m2. Patients required 19.0 [IQR 14.0-27.0] IU/day of basal insulin and 6.0 [IQR 4.1-12.8] IU/day of rapid-acting insulin (total: 0.40 [IQR 0.28-0.49] IU/kg/day). In the first 14-days of FGM, a TIR of 64.0 [IQR 55.5-76.5]% (40%>70%), a time in hyperglycemia of 34.5 [IQR 21.0-44.5] % (35% <25%), and a time in hypoglycemia of 0.0% [IQR 0.0-1.7] (85% <4%, with 0% of the time in glucose < 54 mg/dl) were recorded. The CV was 32.4 [IQR 26.6-36.3]%, the GMI was 7.1% [IQR 6.9-7.7]%, and hypoglycemic events were 1.0 [IQR 0.0-3.5]. A significant higher percentage of time in hypoglycemia was obtained when comparing patients with total pancreatectomy vs other causes (1.5 [IQR 0.7-5.0]% vs 0.0 [IQR 0.0-0.2]%, $P=0.026$), as well as hypoglycemic events (3.5 [IQR 1.5-10.5]% vs 0.5 [IQR 0.0-2.0]%, $P=0.041$). However, there were no differences in TIR (63.5 [IQR 58.7-72.0]% vs 64.0 [IQR 48.5-82.2]%, $P=0.968$), in GMI (7.0 [IQR 6.9-7.4]% vs 7.3 [IQR 6.8-8.0]%, $P=0.437$) or in CV (34.8 [IQR 31.5-42.3]% vs 29.8 [IQR 26.2-35.7]%, $P=0.109$).
Conclusion
Despite the heterogeneous etiology of pancreatogenic DM that influences the pancreas beta cell reserve, we did not find differences in most of the glycemic control parameters. Only the time in hypoglycemia was significantly higher in patients with total pancreatectomy.

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EP441

The closed-loop system in type 1 diabetes management of a pregnant patient: A case report

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Introduction
Managing type 1 diabetes during pregnancy can be challenging. Stricter glycaemic targets are recommended due to maternal and fetal risks. The closed-loop system is an advanced technology more and more commonly used in type 1 diabetes control but rarely reported during pregnancy. We report the case of a patient with type 1 diabetes, treated with the Medtronic 780 G system during pregnancy.
Case Report
A G3P3A0 pregnant patient with type 1 diabetes since the age of 9 years. High glycaemic variability was reported in previous pregnancies when treated with insulin injections. The closed-loop system was activated before the third pregnancy. Pregnancy was reported at 7 weeks. At the beginning of pregnancy, her weight was 45 Kg and glycated hemoglobin (HbA1c) was 6.7%. At week 22, maternal weight was 50 kg, continuous glucose measure (CGM) indicated 70% of the time in range (TIR; 70–180 mg/dl), 5% of time <70 mg/dl, and 25% of time >180 mg/Dl, estimated HbA1C of 7.1% and coefficient of variation of 25%. At week 32, maternal weight was 54 kg, Improved glycaemic control with time spent in different ranges achieved as follows: <70 mg/dl: 1%, 70–180 mg/dl: 94%, and above the target in 5%, estimated HbA1C of 6.3% and a coefficient of variation of 24.3%. During the last month of pregnancy, her overall mean sensor glucose was 134 +/- 32 mg/dl with a coefficient of variation (CV) of 24.2%, and mean HbA1C of 6.5% indicating healthy glycaemic control. Her CGM metrics indicated 92% of the time in range (TIR; 70–180 mg/dl), 1% of time <70 mg/dl, and 7% of time >180 mg/dl. The end of pregnancy took place at week 38 via cesarean section, during which the closed loop was maintained with an 81% TIR, 19% TAR, and no hypoglycemia. In the immediate postpartum period, the automatic mode was not suspended and good glycaemic control was maintained. There were no obstetric complications. The newborn required temporary monitoring in the Neonatal Intensive Care Unit for hypoglycaemia that rapidly resolved within 24 hours. Otherwise, the newborn was healthy, weighting 3840 g. Both mother and baby were discharged on the third day after delivery.
Conclusion
The use of a closed-loop system during pregnancy was associated with decreased episodes of severe hypoglycaemia and better glycaemic control. Further clinical studies on the use of closed-loop systems in pregnancy, delivery, and immediate postpartum should be encouraged.

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EP442

How do people's emotions affect their Diabetes Mellitus?

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Diabetes Mellitus (DM) is, characterized by high blood glucose levels, one of the most common chronic diseases worldwide. In 2021, according to International Diabetes Federation, 537 million adults aged between 20 and 79 are diagnosed with DM. Environmental and genetic factors affect its etiopathogenesis. Disturbances in emotions or emotion regulation are regarded as a major contributor to the pathophysiology and etiology of the disease. People with DM who experience diabetes distress have detrimental emotional effects on self-care and glycemic control. Numerous research has emphasized the impact of people's emotions on DM. In patients with DM, we discovered indications of abnormalities in the emotional identification process, particularly diminished emotional clarity and management, and self-efficacy. People who are capable of managing their DM alone get better health results. It is essential to pay close attention to emotions when tackling a variety of issues in order to improve self-management. The Emotional Freedom Technique (EFT) is one of the interventions used to alleviate psychological distress. It is a brief exposure therapy that combines cognitive and physical components. In this review, we focus on how emotions influence people with DM in their daily lives and the effectiveness of EFT on people with DM.

Keywords: diabetes mellitus, emotional freedom technique, emotional regulation,
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EP443

Are our diabetic patients satisfied with their treatment?

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Introduction
The aim of diabetes treatment is to keep blood glucose levels as near to normal as possible. Training in self management of diabetes forms an essential part of diabetes management. Treatment should be agreed on an individual basiss and

adress medical psychosocial and lifestyle issues. But how much diabetes patients are satisfaied about their treatment?
Materials and Methods
Diabetes Treatment Satisfaction questionnaire (**DTSQs**) was used to measure satisfaction and adherence of patients to their treatment. The questionnaires were filled out anounymously. The first factor assesses treatment satisfaction and consists of six questions (Q1, 4, 5, 6, 7 and 8). These six questions ask about « satisfaction with current treatment », « flexibility », « convenience »,«understanding of diabetes », « recommend treatment for others », and « willingness to continue », respectively. The second factor consists of two questions (Q 2 and 3) wich assess the burden from hyper- and hypoglycemia, respectively.
Results
We submitted 48 patients with type 2 diabetes to the DTSQs questionnaire. The average age of our patients was 56 years. The sex ratio was 0.82.the mean total score of DTSQs (the sum of six questions = 0-36) was 23.85, with the mean score of each question being 3.97. The mean scores of Q2(hyperglycemia) and Q3 (hypoglicemia) were 3.70 and 1.97 respectively.
Conclusion
A number of factors are associated with treatment satisfaction like macrovascular complications actual hypergycemia and specially diabetes education. Self-management education programmes should incorporate this factors to improove the well-bebing of diabetes patients.

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EP444

Dietary habits' assessment in a population of pregnant women with gestational diabetes mellitus

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Introduction
Gestational Diabetes Mellitus (GDM) in a common endocrinopathy during pregnancy. Anectodal evidence suggests that nutritional management of patients with gestational diabetes may reduce the risk of complications. Therefore, the aim of our study were, to assess eating habits in a population of pregnant women with GDM.
Methods
It was a prospective study about 120 pregnant women with gestational diabetes recruited at the Diabetes and Pregnancy Research Unit (UR17SPO2) of Department C In the National Institute of Nutrition of Tunis. We performed an assessment of eating habits followed by a personalized nutritional education.
Results
The mean age was 30 ± 5.17 years with extremes of 20 and 42 years. 48.8% were multiparous. 47.3% had a family history of type 2 diabetes (T2D) and 29.5% a personal history of GDM. Among patients with a history of GDM, only 12% had achieved postpartum glycemic control. The preconception body mass index (BMI) was 29.36 ± 5.1 kg/m^2. Eating habits' evaluation had shown that 91.7% took at least 3 meals a day. The average duration of food intake was more than 15 min in 55% of patients. The most common cooking methods were steam (97%), oven (96%) and grill (96%). Skipping meals was frequent by 43.3% (skipping breakfast: 39.2%; skipping dinner: 29.2%). Skipping meals was linked to a lack of appetite (65.42%) or a time constraint (34.8%). Snacking was found in 72.4% of cases. The consumption of food supplements was noted in 91.6% of cases. They were based on iron (85.7%), vitamin B9 (20.2%) or calcium (17.6%). 47.9% consumed caffeinated drinks, with at least one drink per day for 45.3% of cases.
Conclusion
Eating habits' assessment is essential. Proscribing bad habits such as snacking, caffeinated drinks and systematic consumption contribute to improving the prognosis of these at high-risk pregnancies.

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EP445

Polyglandular autoimmune syndrome type IV with latent autoimmune diabetes of the adult (LADA) and Alopecia Areata - A case report

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Polyglandular autoimmune syndromes (PAS) are a heterogeneous group of rare diseases characterized by autoimmune activity against more than one endocrine organ, although non-endocrine organs can be affected. PAS type IV is a rare syndrome characterized by the association of autoimmune endocrine gland disorder which doesn't fulfill the criteria of PAS type I-III. A 35-years old female diagnosed with alopecia areata and latent autoimmune diabetes of the adult (LADA) one year and respectively two months before her transfer to our outpatient clinic, presented with multiple symtomatic hypoglycemic episodes after initiation of the basal-bolus regim with Glargin U-300 and Aspart insulin in an university diabetes center. The patient stated that the current insulin regim and the recommended carbs intake doesn't fit her work schedule causing huge distress and affecting her daily quality of life. The LADA diagnosis was established based on positive GAD-65, anti-insulin, anti-tyrosine phosphatase-related IA2 antibodies and a normal C-peptide value of 1.36 ng/ml (NV: 0.78-1.89). The labs exams also revealed: Gl = 136 mg/dl, ketonuria (15 mg/dl),mild hypercholesterolemia and A1c = 5.8% (under treatment with Metformin 500 mg/day). The screening for celiac and thyroid autoimmune diseases was negative alongside with the tests for microvascular specific diabetes complications. Based on A1c value and the patient profile, she was switched from basal-bolus regimen to Metformin with progressive dose titration up to 1.5 g/day (maximum tolerated dose) leading to pre-prandial values of 74-101 and post-prandial of 99-200 mg/dl. Also, vitamin D 2000IU/day was recommended from September until May. After 3 months due to a slightly increase in A1c (6.1%) and post-prandial glycemic values (93-236 mg/dl), Sitagliptin 50 mg/day was added leading to a very good glycemic control without hypo events which persists to this day (6 months from initiation). The constalation of one endocrine and one non-endocrine abdnormalities led to the diagnosis of PAS type IV. The good glycemic control obtained by adding a DPP-4 inhibitor to Metformin is in line with the previous reported cases suggesting the benefits of this class in the LADA management.

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EP446

Clinical and genetic profile in a cohort of adults with morbid obesity

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Introduction
There have been more than 130 genes described in relation with the development of obesity, which condition hyperphagia and early obesity. The aim of this study is to determine the prevalence of genetic alterations in a cohort of patients with morbid obesity.
Materials and Methods
We designed a descriptive cross-sectional study for a cohort of subjects with obesity grade III or higher (BMI $\geq$40 kg/m^2), treated at endocrinologist consultations of Hospital Puerta del Mar. In order to determine cases of genetic obesity, an obesity panel has been designed based on exome sequencing of 80 genes.
Results
Preliminarily, we recruited 80 patients, 54 (67.5%) female with a median age of 50 (42-56) years. The maximum weight recorded was 137 (118-158.7) kg. and the maximum BMI was 50.8 (46-56) kg/m^2. Regarding metabolic comorbidities, 39 patients (48.8%) had arterial hypertension, 49 (61.3%) hepatic steatosis, 22 (27.5%) obstructive sleep apnea syndrome, 24 (30%) type 2 diabetes mellitus and 7 (8.8%) impaired fasting blood glucose. A total of 11 (13.6%) patients were diagnosed of hypothyroidism and 6 (7.5%) had history of cardiovascular events. Genetic variants were detected in 48 patients (60%), 33 of them (68.8%) were considered uncertain significance variants, 4 (8.3%) were probably pathogenic variants and 11 (22.9%) were considered pathogenic variants. Regarding the probably pathogenic variants, only a POMC variant [NM_001035256.2:c.638C > T p.(Ala213Val)] with autosomal dominant inheritance could justify the patient's symptoms. The other three

probably pathogenic variants (one in ALSM1, another one in BBS10 and another one in IFT4), all of them with autosomal recessive inheritance, should be considered as carrier patients. Regarding pathogenic variants, a variant in MCR4 [NM_005912.3(MC4R):c.27G>A p.(Met9Ile)] with autosomal dominant inheritance could justify the patient's symptoms, whereas the other variants (one in BBS1, one in CEP290, one in IFT74 and seven in PSCK1) with autosomal recessive inheritance should be considered as carrier patients.
Conclusions
In our cohort, we detected a high incidence of variants, although most of them are uncertain significance variables whereas those that are pathogenic or probably pathogenic should be considered as a carrier status in many cases. Only 2 variants could be considered as a definitive diagnosis of non-syndromic genetic obesity: a variant in POMC [NM_001035256.2:c.638C>T p.(Ala213Val)] and another in MCR4 [NM_005912.3:c.380C>T p.(Ser127Leu)].

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EP447

Menopausal symptoms in postmenopausal women and its association with sarcopenia

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Background and Objectives
With menopausal transition, there is decline in estrogen concentration with potential vasomotor, physical, psychosocial, and sexual health consequences. The loss of muscle mass, strength, and function, known as sarcopenia is common in postmenopausal women. The primary objective of this study is to assess the menopausal symptoms in postmenopausal women and its association with sarcopenia.
Methods
This study was conducted from January to December 2022 in Endocrinology OPD, Ramaiah Hospital, Bengaluru. A total of 106 postmenopausal women with the onset of menopause at >45 years of age were included in the study. Menopausal symptoms, and risk of sarcopenia were assessed with Menopause Rating Scale (MRS) and SARC-F questionnaires respectively. Sarcopenia was defined and assessed according to the Asian Working Group for Sarcopenia guidelines 2019. Data analysis is done with the statistical software SPSS 22.0.
Results
The mean age of the participants was 59.34±7.21 years and the mean age at menopause was 49.50±2.67 years. Majority (80.2%) of the women had high MRS score (moderate-58.5%; severe-21.7%). Among the MRS domains, majority of women had mild somatic symptoms (37.7%), moderate psychologic symptoms (44.3%) and severe urogenital symptoms (60.4%). Urogenital symptoms were significantly high($P=0.002$) in older women. SARC-F score was low in 85.8% and high in 14.2% of women. In our study, 45.3% of women had sarcopenia, 31.1% had possible sarcopenia and 23.6% had no sarcopenia. Women with sarcopenia were significantly older in age($P=0.002$), shorter ($P=0.005$) and their mean weight, BMI were significantly low($P<0.001$). Among women with sarcopenia, majority had mild somatic (41.7%), moderate psychologic (41.7%) and severe urogenital (66.7%) symptoms respectively. Somatic symptoms were significantly severe in women with sarcopenia($P=0.044$). Women with low appendicular skeletal muscle mass index were significantly older and had significantly low hand grip strength and physical performance.
Conclusions
Most of the women (80.2%) had moderate to severe MRS score suggestive of a poor quality of life. Majority of the women (76.4%) had sarcopenia or possible sarcopenia. Most of the women (81.3%) felt they were strong (according to SARC-F score) despite having sarcopenia. There was significant association between somatic symptoms and sarcopenia. There was no significant difference in MRS score or SARC-F score with age. It is essential to assess for sarcopenia in all women ideally during perimenopause and thereby advise for improvement of muscle mass and muscle strength. The limitations of this study are its cross-sectional nature and relatively small sample size.

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EP448

Trends in the prevalence and mortality rate of protein-energy malnutrition in Tunisia

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Introduction
Protein-energy malnutrition (PEM) results from an imbalance between the intake and the needs of the body, which is still noted in developing countries. The aim of this work was to describe the trend of prevalence and mortality rate during the period 2010- 2019 in people aged over 55 years in Tunisia.
Methods
This was a retrospective descriptive study. The data source was the Washington Institute of Health Metrics for Tunisia. We performed a direct standardization of prevalence and mortality rates and analyzed their Trend over 9 years using JointPoint software.
Results
During 2010-2019, the prevalence of malnutrition increased by 9%; the annual average percentage of change (AAPC) was of +1% (95% CI [0.8%-1.2%] for both genders; ($P<10^3$). In the masculine gender the APC was only significant during the period 2017-2019 with a percentage of 4.3% (95% CI [3.1%-5.4%]); $P<0.001$. In contrast, for the female sex we noted a significant APC during the 2 periods 2010-2017 and 2017-2019 respectively of 0.4% (95% CI [0.3%-0.5%] and 3.1% (95% CI [2.3%-4%]) ($P=0.001$). The mortality rate showed a clear decrease of -18% with a AAPC of -1.8 (95% CI [2.3%-1.4%] significant for both genders ($P<0.001$).
Conclusion
Even if the ECD mortality rate in Tunisia has decreased during the last decade owing to early diagnosis, the prevalence still notes a significant increase. This underlines the importance of an adequate nutritional management.

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EP449

Sulfite oxydase deficiency encephalopathy: Description of a new pathogenic mutation in SUOX gene

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Sulfite oxidase deficiency encephalopathy is a rare genetic disease, secondary to the mutation of the SUOX gene, which codes for the enzyme sulfite oxidase that catalyzes the oxidation of sulfite to sulfate, an essential process for the catabolism of sulfur amino acids. This rare disease is characterized clinically by seizures, progressive encephalopathy and lens dislocation. The objectives of this report are to describe the clinical, paraclinical and evolutionary characteristics of this pathology, as well as the interest of prenatal and pre-implantation diagnosis in its management. This case involved a first-degree relative referred to the medical genetics department because of a personal history of 3 neonatal deaths in their offspring, at d6, d5 and d21 of life respectively, in a picture of epileptic encephalopathy appearing 12 hours after birth. The 3 pregnancies were well followed, carried to term, without any notion of acute fetal suffering, infectious syndrome or toxic intake. The newborns had normal birth weight and Apgar score, and no malformative or dysmorphic signs. A brain MRI could be performed in the last child and showed a T2 hypersignal of the supratentorial white matter, an arachnoid cyst of the posterior cerebral fossa, and hypoplasia of the cerebellum. Since no genetic analysis could be performed in the 3 newborns, and in view of the clinical and paraclinical picture suggesting an inborn metabolic disorder and the notion of 1st degree consanguinity, a high-speed sequencing of the exome of both parents was requested. A missense mutation NM_000456.2:c.1187A>G p.(Gln396Arg) of unknown significance (class 3) in the SUOX gene was found in the heterozygous state in both parents. In addition, a pathogenic missense mutation (class 1) of the TTC21B gene was found incidentally in the heterozygous state in the father. This mutation is responsible for hereditary nephronophthisis in the homozygous state. Given the family history

and the results of genetic tests, the diagnosis of encephalopathy by sulfite oxidase deficiency by homozygous mutation of the SUOX gene was retained. This rare genetic disease, of unknown prevalence, is transmitted by autosomal recessive mode. Thus, the risk of recurrence for this couple is 25%. This explains the interest of genetic counselling, in order to propose a prenatal or pre-implantation diagnosis to the couple, and a search for the mutation in relatives at risk.

Keywords: encephalopathy by sulfite oxidase deficiency, SUOX gene, prenatal diagnosis, pre-implantation diagnosis.

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EP450

Combination of mutations in the HNF1A and ABCC8 genes: clinical polymorphism in members of the same family

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Mutations in HNF1A gene underlie the development of maturity onset diabetes of the young type 3 (MODY3). Mutations in ABCC8 gene are the cause of neonatal DM and the rare MODY12, which is clinically similar to MODY3. In these forms of MODY, there is a high sensitivity to sulfonylurea, but over time, patients may need insulin therapy.

Patient A, 17 y.o. He was born to woman with gestational DM. At the age of 12.5, fasting hyperglycemia of 13 mmol/l was detected. Insulin therapy was not prescribed due to the parents refusal. At the 14.5 y.o, since his mother was diagnosed with MODY3, a pathogenic variant p.R54X in HNF1A was detected, a MODY3 was diagnosed. At the age of 15, he was hospitalized with hyperglycemia 13.8 mmol/l. HbA1c - 9.8%. Long-acting insulin was assigned. Subsequently, the patient used insulin irregularly and consumed large amounts of fast carbohydrates. His maximum HbAc1 was 20.5%. At 17 y.o, he was admitted to hospital: glycemia was 18.6 mmol/l, HbAc1 - 12.6%, islet antibodies were negative. Intensified insulin therapy (0.9 units/kg/day) led to the normalization of glycemia. Specific diabetic complications were not detected. In addition to the variant in the HNF1A, a p.R521X variant was found in the ABCC8. After 3 months, the boy was successfully transferred to glibenclamide 7.5 mg/day.

Patient L, 37 y.o, proband's mother. At the age of 20, gestational DM was diagnosed: fasting glycemia was 6-9 mmol/l, she refused insulin therapy. At the 32 y.o, an examination for cholelithiasis revealed hyperglycemia, the variant p.R54 X in the HNF1A was detected. To date, she has not received hypoglycemic therapy, followed a carbohydrate-restricted diet. At the last examination at the age of 37, HbAc1 was 6.7%, a variant of p.R521X was found in the ABCC8 as in the son.

Patient S, 8 y.o, proband's sister. HbAc1 – 5.4%, fasting glycemia – 4.7 mmol/l. There are variants of p.R54X in the HNF1A and p.R521X in the ABCC8.

Conclusion

MODY associated with variants in the HNF1A and ABCC8 is characterized by a different degree of carbohydrate metabolism disorders, depending on the location of mutation in gene and its severity. We have presented a description of clinical polymorphism in members of family with a combination of identical mutations in the two MODY genes. The more severe disease in proband, apparently, is due to the low compliance. Normoglycemia in sister may be due to age, which requires further dynamic observation.

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EP451

Severe hypoglycemia in non-diabetic patients

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Introduction

Non-diabetic hypoglycemia (NDH) is defined by a glycemia <0.50 g/l with the presence of neuroglycopenic signs and their disappearance after glucose administration.

Objective of the Study

Describe the diagnostic and therapeutic aspects of severe NDH cases in our department.

Material and Methods

Over a period of 12 years (2010 – 2022), 32 patients met the definition criteria.

Results

The average age of our patients was 48.4 years, with a female predominance (76.3%). Hypoglycemia was recurrent in 81% of cases with an average capillary blood sugar of 0.32 g/l occurring in a fasting state in 67% of patients and in post-prandial in 33% of cases. The fasting test carried out in 24 patients, with an average duration of 15.2 hours, pointed to an organic cause in 65% of cases with complementary imaging: pancreatic CT (34.1%), abdominal MRI (25%), CT angiography (6.7%), echo-endoscopy (28%), chest CT (3.1%) and pituitary MRI (3.1%). The different etiologies found were: an insulinoma (14, malignant in 2 cases), factitious hypoglycemia (6), an extrapancreatic tumor secreting IGF2 (4), functional hypoglycemia (6), nesidioblastosis (1) and corticotropic insufficiency (1).

Discussion

These results summarise the severity of NDH with female predominance.

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EP452

Non-islet cell tumour hypoglycaemia (NICTH)

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An 87-year-old lady was admitted to hospital with severe unexplained hypoglycaemia with capillary glucose of 1.8 mmol/l and went on develop recurrent episodes of symptomatic hypoglycaemia during this admission. She had a background history of diabetes mellitus, well under controlled with diet and a previous diagnosis of solitary fibrous pleural tumour of left lung, which was resected completely in 2013 but reoccurred in 2022 with left sided pleural effusion. Her liver and renal function tests were within normal reference range. She has a normal cortisol response to synacthen test as follows: 335nmol/l at zero minutes,955 nmol/l at 30 minutes and 1066nmol/l at 60 minutes. CT chest showed a 22 cm solid lesion in the left hemithorax, which had enlarged, considerably in comparison with previous scans and represented a recurrence. Laboratory assessment during one of the hypoglycaemic episodes (venous glucose 1.3 mmol/l (3.6-5.4)) revealed a C-peptide of 25 pmol/l(normal range 370- 1470) and insulin level of $<$ 12 pmol/l (normal level 18-173). Paraneoplastic hypoglycaemia likely due to NICTH was suspected, however insulin like growth factor 2(IGF-2) level could not be processed due to unavailability of radiolabelled assay. She was deemed an unsuitable candidate for further operation and chemotherapy by the lung multi-disciplinary team .An initial attempt to treat hypoglycaemia with a tapered dose of prednisolone failed, so she was continued on oral prednisolone 15 mg once a day. Unfortunately, hypoglycaemia (capillary blood glucose 1.7 mmol/l) re-occurred and she was re-admitted to hospital and Prednisolone dose was increased to 30 mg once day. If this fails Growth hormone injection will be next available treatment option for her although her prognosis is poor in view of the advanced neoplastic disease.

Discussion

- NICTH is a rare cause of paraneoplastic hypoglycaemia and is mostly seen in mesenchymal and epithelial tumours.
- It is due to an underlying tumour producing excessive IGF-2 or pro IGF-2.
- It can cause profound and persistent hypoglycaemia and may not respond to medical treatment and the main stay of treatment is surgical excision of underlying tumour.

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EP453

High blood pressure in obese patients: body composition and dietary patterns

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Background and Aim
Obesity is a major risk for the development of hypertension.These cardiovascular risk factors are associated with nutritional targets. The aim of our study was to determine clinical characteristics,body composition and hypertension-related dietary patterns of obese patients with high blood pressure.
Methods
This was a cross sectional study including 70 patiens. Clinical characteristics, anthropometric measures were collected. Body composition was determined by Bioelectrical impedance analysis. Adjusted body weight (ABW) was calculated for all patients. Dietary intake data were collected by trained nutritionists using a 24-hour recall method.Patients were divided into 2 groups: Group1 (G1) consists of 43 obese patients without hypertension and groupe2 (G2) consists of 27 obese patients with hypertension. Clinical caracteristics,anthropometric measures,body composition and dietary intake were compared between the two groups.
Results
Mean age was significantly higher in G2 patients (55.33 $\pm$ 13.4 vs 38.81 $\pm$ 15.4; $P<10^{-3}$). Prevalence of diabetes, dyslipidemia and obstructive sleep apnea syndrome was signifiantly higher in G2 patients($P=$ 0.03; $P=0.002$;$P<10^{-3}$, respectively). Mean Body Mass Index and waist circumference did not statistically differ among the two groups($P=$ 0.3 and $P=$ 0.5, respectively). Body water percentage was significantly higher in G1 patients (42.73% $\pm$ 6.1 vs 39.54% $\pm$ 4.25; $P=$ 0.04) while lean mass, skeletal muscle mass and fat mass percentage did not statistically differ among the two groups (76.95 kg $\pm$ 11.11 vs 55.92 kg $\pm$ 7.39; $P=0.39$, 53.04 kg $\pm$ 9.1 vs 56.44 kg $\pm$ 11.34; $P=0.2$ and 43.31% $\pm$ 11.24 vs 42.51% $\pm$ 8.43; $P=$ 0.78, respectively). Mean saturated fatty acid intake and total fat intake were significantly higher in G2 patients (9.68% Total energy intake (TEI) $\pm$ 2.99 vs 8.1% TEI $\pm$ 2.92; $P=$ 0.015 and 1.58 g/kg ABW $\pm$ 0.68 vs 1.18 $\pm$ 0.5 g/kg ABW; $P=0.02$, respectively). Fiber intake and simple sugar intake and protein intake did not statistically differ among the two groups ($P=$ 0.4, $P=$ 0.2 and $P=$ 0.1, respectively). G1 patients had significantly higher magnesium intake (395.55 mg/d $\pm$ 278 vs 291.71 mg/d $\pm$ 101.07; $P=0.04$) , iron intake (12.92 mg/d $\pm$ 9.16 vs 8.9 mg/d $\pm$ 2.64; $P=0.01$) and calcium intake (792.12 mg/d $\pm$ 305.79 vs 549.64 mg/d $\pm$ 195.25; $P=$ 0.005) compared to G2 patients. Sodium, potassium and sodium/potassium ratio did not statistically differ among the two groups ($P=0.07$; $P=0.09$ and $P=0.1$, respectively).
Conclusion
This study shows inappropriate nutritional habits in patients with hypertension, related to the coexistence of obesity.Our results are in line with other studies. Patients should be guided to choose more low-fat dairy products and other low-fat calcium sources and to increase intakes of magnesium.

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EP454

Does the prebiotic and probiotic supplementation influence the lipid profile of obese patients?

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Background
The role of gut microbiota on our health is increasingly well known. It plays a role in digestive, metabolic, immune and neurological functions. The objective of our work was to evaluate the effect of prebiotic and probiotic supplementation on the lipid profile in addition of a weight loss program.
Methods
This is an interventional study involving 45 obese patients consulting the obesity unit of the Institute of Nutrition of Tunis during the period from May to August 2022. Patients were divided into 3 groups matched for age, sex and BMI: diet alone, prebiotics (30g of carob/d) and probiotics (1 tablet of Lactibiane*/d). The lipid profile (total cholesterol (TC), triglycerides (TG), HDL-c and LDL-c) was performed at T0 and at one month after the intervention (T1).
Results
The mean age was 48.73 $\pm$ 7.7 years with a female predominance (93.3% of women). There was a significant decrease in total cholesterol (-0.4 mmol/l) and LDL-cholesterol (-0.3 mmol/l) for the diet alone group between T0 and T1 ($P=0.03$ and 0.05 respectively). For the prebiotic group we noted a significant decrease in total cholesterol (-0.4 mmol/l), LDL-cholesterol (-0.4 mmol/l) and TG (-0.5 mmol/l) ($P=0.005$, $P=0.003$ and $P=$ 0.001 respectively). For the probiotic group, there was a significant decrease in plasma levels of total cholesterol (-0.7 mmol/l) and triglyceride (-0.3 mmol/l) ($P<0.001$ and $P=0.006$ respectively). There was no significant improvement in HDL-c levels in the three groups. For the comparison between groups: The three groups were comparable for improvement in total cholesterol. The prebiotic and diet alone groups were comparable for improvement in LDL-c ($P=0.4$) and the prebiotic and probiotic groups were similar for improvement in TG ($P=0.2$).
Conclusion
The improvement of total cholesterol and LDL-c was not related to the use of symbiotics. On the other hand, the use of symbiotics seems to improve triglyceride levels with a comparable effect for prebiotics and probiotics.

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EP455

Features of psycho-emotional status and quality of life in patients with metabolic syndrome

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Metabolic syndrome (MS) is characterized by obesity, hypertension, dyslipidemia, and insulin resistance. The severity of the clinical manifestations of MS affects the quality of life (QoL) of patients, while indicators of physical and mental health decrease. In patients, anxiety and depressive disorders in 80-90% of cases are latent, which can aggravate the course of the underlying disease. The purpose of our work is to study the psycho-emotional status and quality of life in patients with metabolic syndrome.
Research Methods
The study was conducted on the basis of the clinic of the Scientific Research Institute of Medical Problems of the North FRC KSC SB RAS. All patients were divided into groups: group 1 - 76 patients with MS, group 2 - 42 practically healthy volunteers without concomitant diseases and not obese. Patients were examined with determination of anthropometric parameters: waist circumference (cm), body weight (kg), BMI (kg/m^2). The assessment of the quality of life was determined using the SF-36 questionnaire. The level of anxiety and depression was assessed in points according to the hospital anxiety and depression scale HADS (1983).
Results
According to the obtained results, the majority of QoL indicators differed statistically significantly in the group of patients with MS relative to the control group (Group 2). Thus, the indicators of the level of QoL are significantly higher in healthy individuals than in patients with obesity. Differences in all groups are significant ($p \leq 0.05$). It was also found that a decrease in the average level of parameters on the scale "physical functioning" by 19.7% ($P<0.05$), "role functioning" by 35.2% ($P<0.05$), "general health" by 15, 1% ($P<0.05$), "vitality" by 18% ($P<0.05$), "emotional functioning" by 53.1% ($P<0.05$). The assessment of the level of anxiety and depression in patients with MS corresponded to a subclinically expressed level, and the level of depression exceeded the indicator of the control group (Group 2) by 19.3%. The level of QoL in patients with obesity is significantly lower than in healthy individuals.
Conclusion
The obtained results show that in patients with MS, quality of life indicators decrease, most patients have significant changes in the state of the psycho-emotional sphere, subclinical anxiety-depression is determined. Also, patients require correction of psychological disorders, which will reduce the level of anxiety and depressive disorders, which will further improve the quality of life.

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EP456

Comparison of symptoms and clinical complaints in people with various manifestations of metabolic syndrome

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Introduction
Metabolic syndrome (MetS) is combined groups of diseases with common pathogenesis and clinical signs and symptoms. Usually MS starts with obesity and last step appeared as a Diabetes Mellitus. We aimed to compare clinical signs and patients complaints according to type of manifestation of MetS.
Material and Methods
Patients data, clinical complaints, anthropometric, biochemical parameters in 248 patients with various manifestations of the MetS, such as obesity, impaired glucose tolerance (IGT), polycystic ovary syndrome (PCOS), type 2 diabetes mellitus (DM2).
Results
The age of patients was important as a risk factor for the development of various manifestations of MetS. In particular, patients with PCOS were the youngest, and in the direction of obesity, IGT and DM2 the age were getting older. The BMI was higher in all patients with MetS, which indicated higher body weight in all groups. In particular, BMI was highest in obesity group (42.83 kg/m^2), followed by IGT (36 kg/m^2), PCOS (34.6 kg/m^2), DM2 (32.34 kg/m^2). Analysis of patients' complaints made it possible to identify those that specific for manifestation forms of MetS. In particular, for DM2 the presence of dry mouse, thirst, frequent urination, weakness, dry skin were specific, whereas excessive food intake, weight gain, dyspnea were shown in IGT and obesity, excessive skin hairiness, infertility, menstrual cycle irregularities are more pronounced in PCOS, that could facilitate the identification and differential diagnosis of type of MetS manifestation in overweight or obese individuals in medical practice.
Conclusion
People age was main risk factors in the development of MetS where patients with PCOS were younger and getting older in direction to Obesity, then IGT and DM2. Comparing of BMI showed that it was higher in Obesity group and lowered into direction of IGT, PCOS then DM2. Comparison of people complaints revealed specific for various manifestation of MetS that will help in identification of type of MetS in people with obesity.

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EP457

Assessment of physical activity levels in a population of obese patients

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Introduction
The health benefits of physical activity have been demonstrated in many diseases, including obesity. The aim of our study was to assess the physical activity level of obese patients.
Methods
A prospective cross-sectional study was conducted on 55 obese patients who consulted the obesity unit of the National Institute of Nutrition in Tunis between March and July 2022. The level of physical activity was assessed by the Ricci and Gagnon questionnaire, which defines an active profile for a score $\geq$18 points.
Results
The average age was 47 years (14-79) with a female predominance (82%). The average weight was 99 $\pm$ 19 kg with an average BMI of 38 $\pm$ 6 kg/m^2. The average waist circumference was 116 $\pm$ 15 cm. Of the patients included, 10 were active (18%) and 45 were inactive (82%). The average Ricci and Gagnon score reported by the patients is 13.5 $\pm$ 6.9, which is considered inactive. Men were more active than women (P = 0.04). Physical activity was associated with fewer articular complications (P = 0.02). Physically inactive patients had higher BMI (37 kg/m^2 vs 36 kg/m^2, P = 0.04) and higher waist circumstance (117 cm vs 113 cm, P = 0.1). *Physical activity* was associated with better sleep quality assessed by *the Pittsburgh Sleep Quality Index* (P = 0.03). Physically active patients had higher HDL cholesterol (1.3 g/l vs 1.1 g/l, P = 0.04) and lower fasting blood glucose measure (7.6 mmol/l vs 8.6 mmol/l, P = 0.5).
Conclusion
The majority of patients were inactive. Physical activity was associated with a better anthropometric and glycaemic profile, higher HDL cholesterol, and better sleeping quality. These results underline the importance of physical activity in the treatment of obesity. The prescription should be based on an analysis of daily physical activity, medical situation, motivation, barriers, and risks in order to develop an individualized and adapted program for each patient.

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EP458

A simple score for predicting non-alcoholic fatty liver disease in obese patients

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Introduction
Non-alcoholic fatty liver disease (NAFLD) represents the most common and fastest growing liver disease. Its incidence is associated with the global obesity epidemic.
Objective
To develop a simple score to predict the risk of NAFLD in the obese patient.
Methods and Materials
This is a descriptive cross-sectional study including 95 patients who consulted at the Human Obesity Research Unit of the National Institute of Nutrition in Tunis. Patients were interviewed, anthropometric measurements (weight, height, body mass index (BMI), waist circumference) were taken, biological assessment (fasting blood glucose, triglyceride, total cholesterol, HDL-cholesterol) and abdominal ultrasound were conducted to look for hepatic steatosis.
Results
The mean age of our patients was 48.7 $\pm$ 7 years with a female predominance (91.6%). The mean BMI was 41 $\pm$ 13 kg/m^2. The mean waist circumference was 114 $\pm$ 8 cm. The frequency of hepatic steatosis was 70.5%. In univariate analysis, the following NAFLD risk factors: BMI, waist circumference, waist-to-height ratio $\geq$0.7 and triglyceride/HDL cholesterol ratio $\geq$2.5 were all correlated with hepatic steatosis with a statistically positive P (P < 0.05). In multivariate analysis, only waist-to-height ratio $\geq$0.7 was independently associated with NAFLD with an adjusted Odds Ratio of 4.1 (P = 0.03).
Conclusion
Waist-to-height ratio $\geq$0.7 is an independent risk factor for NAFLD in obese patients. It is a simple parameter that can be used in routine practice as a screening tool for non-alcoholic fatty liver disease.

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EP459

Evaluation of cardiovascular risk and use of arterial age in an obese Tunisian population

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Introduction
The objective of our study was to calculate the risk of cardiovascular event and arterial age in an obese Tunisian population.
Methods
This is a cross-sectional study conducted in service A of the National Institute of Nutrition in Tunis. 25 patients were included. The score from The Framingham Heart Study(1) was used to calculate cardiovascular risk and arterial age.
Results
The mean age was 44.28 + 13.2 years, the average duration of obesity was 20.8 + 10.4 years, the mean BMI was 47.9 + 9.2 kg/m^2, average waist circumference was 134.01 + 18.48 cm, the mean arterial age was 53.12 + 18.59 years. High blood pressure, Type 2 Diabetes, smoking, hypercholesterolemia and Low HDL cholesterol were noted in 40%, 34%, 20%, 46%, 23% of patients respectively. A cardiovascular risk higher than 10 was noted in 32% of population (n = 8). The analytical study showed a significant difference between chronological age and arterial age (P = 0.001). Arterial age and cardiovascular risk were not correlated with BMI or waist circumference or duration of obesity progression.
Conclusion
Our study has shown that cardiovascular risk stratification is possible on simple clinical-biological data. Obesity increases the cardiovascular risk mainly through its complications, hence the interest of repeating the cardiovascular evaluation at each consultation in order to improve the vital prognosis in this population.
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EP460

Complications of obesity: a retrospective study of a Tunisian population

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Objective
To study the characteristics of obesity in a Tunisian population and determine the associated complications.
Methodology
Retrospective study including 60 obese patients followed at the obesity unit of the National Nutrition Institute of Tunis.
Results
The mean age was 44 ± 11.08 years with a female predominance of 87%. The average body mass index (BMI) was 35.7 ± 4.8 kg/m^2. Obesity class I, class II and morbid obesity were observed in 51.7%, 30% and 18.3% of cases respectively. Sleep apnea syndrome was noted in 26.7% of patients. It was significantly more frequent in cases of morbid obesity than in the other classes ($P=0.001$). High blood pressure was present in 22.4% of the population without significant difference according to the severity of obesity ($P=0.21$). Metabolic complications were dominated by hypoHDLemia (56.9%), glucose intolerance (31%), hyperuricemia (27.6%) and hypertriglyceridemia (22.4%). Only the association of hyperuricemia with class III obesity was statistically significant ($P=0.006$). Digestive complications were dominated by hepatic steatosis in 25% of obese patients. It was significantly more present in cases of morbid obesity ($P=0.003$). Osteoarticular complications were present in 51.7% of cases with no statistically significant difference according to BMI.
Conclusion
Complications of obesity, especially morbid, were frequent in our population. This imposes the implementation of preventive measures as well as an adequate management of this pathology.

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EP461

About 2 rare cases of morbid obesity with syndromic character

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Introduction
Bardet-Biedl syndrome (BBS) is a rare disorder. It is an autosomal recessive hereditary ciliopathy, including: Multivisceral impairment, associated with obesity, learning disabilities, with or without intellectual deficit. We report the observation of 2 patients followed in our training for morbid obesity.
Case Report
Case 1: O. Y. 17 years old, from a non-consanguineous marriage. Admitted for management of morbid obesity, BMI = 70 kg/m^2, Malformative syndrome: [Postaxial hexadactyly of the 4 limbs, Club feet, Ogival palate]. Ophthalmologic anomalies: [Nystagmus, Strabismus]. Neurological examination: [Coordination disorders]. Paraclinical check-up: Eye fundus: retinitis pigmentosa, Standard radiography: Hexadactyly of the 4 limbs with club feet. Abdominal ultrasound: a left upper polar renal cyst. The biological workup was unremarkable, apart from a vitamin D deficiency that was being corrected.
Case 2: A.F. 15 years old, from a non-consanguineous marriage. Admitted for management of morbid obesity.BMI = 40 kg/m^2, Malformative syndrome: [brachydactyly of both hands, club feet]. Ophthalmologic anomalies: [Strabismus]. Paraclinical check-up: Fundus: retinitis pigmentosa, standard X-ray: brachydactyly of both hands with club feet, abdominal-pelvic ultrasound: no genitourinary malformation. The biological workup was unremarkable.
Discussion and Conclusion
BBS is an inherited ciliopathy resulting in multivisceral involvement and intellectual deficit. The diagnosis of BBS is clinical and defined by the association of four major criteria or three major and two minor criteria according to Beales et al. The diagnosis of BBS was made in the first patient because of the first four major criteria, which were also associated with three other minor criteria: strabismus, coordination disorder and ogival palate. In the second patient, the diagnosis was based on 3 major and 2 minor criteria. The medical management of BBS is multidisciplinary because of the multivisceral involvement

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EP462

Eating Habits of Obese Patients: One obesity center Experience

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Introduction
Obesity is a component of eating disorders grouped under several eating disturbances due to emotional problems. Eating habits are directly influenced by eating disorders. Eating disorder rates in obese patients are reported to be 15-50% in various populations. This study aimed to evaluate obesity related eating habits (OREH) in obese patients who followed in an obesity center.
Methods
A total of 752 (F/M: 636/116, 42.6 ± 11.6 yrs) obese patients (BMI > 30) who applied to the Obesity Center of Marmara University Pendik Education and Research Hospital (ERH) were included in this cross-sectional study. Obesity is classified as Stage 1 (BMI 30-34.9), Stage 2 (BMI 35-39.9), and Stage 3 (BMI > 40). We evaluated graze eating, night eating, eating addiction, and binge eating in the context of OREH in accordance with the literature. Self-report tests including The Short Inventory of Grazing (SIG), Modified Yale Food Addiction Scale (mYFAS), Night Eating Questionnaire (NEQ), Emotional Eating Scale (EES), and Binge Eating Scale (BES) were given to the patients. OREH results were determined based on these test's cut-off points.
Results
Mean BMI was found to be 42.1 ± 6.6 kg/m^2. There were no statistically significant difference between both genders in respect of age and BMI ($P > 0.05$). Mild grazing habits was observed in 136 (18%) cases, moderate grazing in 309 (41%) cases, and severe grazing in 229 (30%) cases. Modarete stage grazing was more common in women (265, 41.6%) and men (44, 47.6%). Binge eating was recorded in 337 of the total (44.8%) patients, in 287 of women (45.1%) and 50 men (43.1%). Emotional eating was present in 113 of the total patients (15%), in 103 of women (16.1%) and 10 men (8.6%). Food addiction were seen in 402 of all cases (53.4%). High stage food addiction was more common in women (169, 51.1%) and men (30, 42.2%). Night eating was found in 225 patients among all (29.9%) with 185 (29%) to be in women and 40 (34.4%) in men. Emotional eating ($P=0.032$) and night eating ($P=0.025$) were found to be statistically significant in regard of BMI.
Conclusion
In this cross-sectional study, many of obese patients had obesity related eating habits whereas 65% of all cases had more than one component of obesity related eating habits. Determining the eating disorders prior to obesity treatment are necessary for planning and treatment compliance.

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EP463

Analysis of covid inpatients lethality in adults with metabolic disoders such as diabetes and/or obesity

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COVID-19 significantly influenced global mortality; it caused 6.6 million cases of death. Mortality or crude death rate (CDR) is a typical statistical value for analyzing the demographic processes among the population. In Ukraine, we observed an increase in CDR in 2020-2021. It could be caused directly by the COVID-19 pandemic and indirectly; due to social distancing. Some people avoid visiting a doctor and neglect their treatment of chronic diseases. Comorbidities such as obesity could lead to the rapid progression of COVID-19, especially in the presence of a 'deadly triad' (Lim S. et al., 2020) as age, male gender, and access to adiposity in the body). We decided to check the influence of obesity on the outcome of COVID-19 hospitalization. The research aimed to find the correlation between BMI and laboratory findings such as C-reactive protein and interleukin-6. We researched inpatients with COVID-19 and metabolic disorders to determine whether obesity influenced the inflammatory process and caused poor outcomes with a high probability of acute respiratory distress syndrome; the obtained data from the performed research approved that hypothesis. We analyzed 130 cases of hospitalization due to COVID-19 in the Medical Centre Universal Clinic "Oberig" in 2020-2021. We compared the group of inpatient survivors ($n=90$) and non-survivals ($n=42$). The mean age was 81 years (CI 78-84) and 79 years (CI 70-81), correspondingly ($P<0.001$). In previous studies, we found that the frequency of obesity raised to. We compared several parameters, such as the minimal absolute lymphocytes count that was observed during hospitalization (0.56 (0.4-0.9) and 0.19 (0.1-0.28), $P<0.001$); the highest C-reactive protein (CRP) (37.57(17.06-72.97) and 120.98 (75.21-179.6), $P<0.001$); baseline IL-6

(23.5 (9.1-43.4) and 33.4 (17.7-74.9), $P=0.008$); baseline ferritin (328 (154-558) 735 (415.5-1175), $P<0.001$). Mean Hb1Ac was 5.26% (4.78-5.87) and 5.5 (4.98-6.52), $P=0.089$). According to the received data, we calculated the correlation between BMI and the highest CRP (Ro = 0.512), $P=0.01$.); between BMI and baseline IL-6 (Ro = 0.686, $P<0.01$); between severity of respiratory insufficiency and minimal lymphocyte count (Ro = -0.598, $P<0.01$).
Conclusion
the paper is devoted to solving a significant scientific and practical problem of individual assessment of COVID-inpatients on the presence in them of high inflammatory rates, especially in the case of diabetes and obesity comorbidity as it could influence mortality and could be associated with poor prognosis.
Keywords: metabolic disorders, obesity, aging, IL-6, COVID-19, pandemic, public health, risk factors.
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EP464

Overweight and Obese Indians' Attitudes Toward Obesity, Willingness to Lose Weight, and Treatment Preferences
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Obesity has become a major health concern around the world, and it is linked to a variety of diseases and complications. Losing weight is an effective strategy for lowering BMI and avoiding the complications of obesity. However, weight loss is determined by an individual's attitude toward obesity as well as their willingness to lose weight.
Aim
To investigate attitudes toward obesity, willingness to lose weight, and treatment preferences among Indians who are overweight or obese. An analytical cross-sectional study was carried out among overweight and obese Indians. The study was carried out using a self-administered questionnaire from December 2021 to November 2022. Inclusion Criteria: 1. Obese by WHO guidelines 2. willing to be a part of the study. The results showed that 78.5% of the 327 participants were unhappy with their current body weight. Controlling chronic disease was a major motivation for losing weight (57.2%), and exercise and diet were the most preferred methods of losing weight. Age is an important factor in deciding attitude towards obesity. ($P=0.0001$).
Conclusion
Participants in the current study reported high levels of dissatisfaction with their current weight and a willingness to lose weight. Health workers should focus on talking and informing more about obesity as they will encounter an large number of these patients in opd.
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EP465

Abstract withdrawn
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EP466

Barriers of adaptations with psycho-social problems in type 2 diabetes
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Type 2 diabetes is a progressive chronic disease that is on a global upward trend and involves high healthcare costs. Obstacles to adaptation to this disease include knowledge of the disease, fear of treatment, inability to adapt to changes in lifestyle, lack of physical activity and exhaustion. Type 2 diabetes significantly affects brain function, including cognitive function, and increases the risk of depression. The studies reveal that there has been no comparison of neurological changes in healthy people over the lifespan experienced by diabetics of the same age. Cognitive dysfunction mechanisms are multifactorial. It is affected by age, disease duration, HbA1c, comorbidities and medications. Depression is a very common problem in type 2 diabetes and has a multi-directional effect. Depression can trigger type 2 diabetes and develop depression in type 2 diabetes. The mental health problem worsens coping, and quality of life and increases mortality rates. Depression is often undiagnosed or inadequately treated for this disease. Psychosocial problems include a person's attitudes towards diabetes, expectations of treatment and outcomes, mood changes, available resources, and psychiatric background. To detect early symptoms of depression, we can use non-invasive methods, one of which is brain ultrasound. For an objective assessment of sleep disorders, it is possible to use melatonin determination in urine, which is simple and easily available. The purpose of the study is to examine the changes in the raphe nuclei in the brain, melatonin levels in urine, along with mental health and sleep quality questions and comprehensive background data in people with type 2 diabetes. A double-blind controlled study of barriers to adjustment to illness in people with type 2 diabetes. The sample consists of ($n=600$) people with type 2 diabetes and their relatives in the control group. Data are collected during one year from the regional hospital and private health center included in the study. As a result of the study, we get evidence of the changes in the Raphe nuclei of the brain for comparison with the results of the Moca test, and the change in the melatonin level in cognitive disorders in people with type 2 diabetes.
Keywords: type 2 diabetes, adaptation barriers, psychosocial problems, complications, depressioon, cognitive impairment
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EP467

"Knowledge, Beliefs, and Practices of People with Type 2 Diabetes toward Self Management and Diabetic Foot"
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Introduction
Diabetic foot is a physio pathological state with an etiopathogenic neuropathic basis, induced by sustained hyperglycaemia in which, with or without the co-existence of Peripheral Arterial Disease, and with a prior triggering trauma, ulcers and/or deep tissue destruction occur on the feet of diabetics.
Objectives
To evaluate the knowledge, beliefs, and practices regarding diabetes and its complications among Omani type 2 diabetes patients.
Patients and Methods
A cross-sectional study enrolled 150 participants from the Diabetes Clinic at Bausher polyclinic, Muscat. Data was collected using questionnaires.
Results
Only 38% checked their feet regularly and only 5.6% were having diabetic foot. The practices regarding physical activity and blood glucose monitoring were found to be poor. results were as follows 84% don't know the cause of diabetes also 37.3% don't know the complications of the same while 55.3% don't know cause of diabetic foot and 50% don't know the symptoms of diabetic foot.
Conclusions
Educational interventions that approach the adoption of essential behaviour with regard to foot care are considered the ideal practices for this public, which should include daily foot examination and preventive care for skin, nails and callosity. Professionals should incorporate the practice of health-related education in their daily routines to better assist their patients. Furthermore, as those responsible for promoting, protecting and recovering health, they are expected to obtain desirable results with diabetics in preventing and delaying the onset of foot complications and help diabetics to improve their quality of life.
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EP468

Lipid metabolism in patients type 1 and type 2 diabetes mellitus combined with Ischemic heart disease
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Diabetes mellitus with characteristic high blood serum glucose may cause various disorders, including damages to blood vessels. Both type 1 and type 2 DM increase the IHD risk by 4-6 times. The work was initiated to study parameters of lipid metabolism in patients with the IHD-combined type 1 and type 2 DM.
Materials and Methods
We examined concentrations of total lipids, triglycerides (TG), total cholesterol (TC) and high density lipoprotein cholesterol (HDL C) in 58 patients with

diabetes mellitus. 20 patients had diabetes mellitus without IHD, 8 and 12 persons with type 1 and type 2 DM, respectively, among them. In 38 patients DM was combined with IHD.
Results and Discussion:
Total lipids, TC and TG were found increased in all patients, but the ratios varied by the DM type. TC concentrations were approximately identical in all groups of patients, while those of TG, TC and HDL C were found to change by the DM type and presence of IHD. The most significant changes in the TG concentrations were observed in the blood serum of the patients with type 2 DM in combination with IHD (286.0±27.5 mg%); the concentrations in patients with type 2 DM without IHD were similar to those in the controls (139.3±0.3 mg%). The highest mean level of total lipids was measured in patients with the IHD-combined type 1 DM (11.42±0.61 g/l).The HDL C concentrations were found reduced in most patients, being more significant in those with the IHD-combined type 1 DM. In patients with the IHD-combined type 2 DM, concentrations of TC, TG and HDL C were higher than those in the patients with the IHD-combined type1 DM. In patients with the IHD-combined type 2 DM, concentrations of total lipids, TC and TG were higher than those in the diabetic patients without IHD, while concentrations of HDL C were found lower. Concentrations of total lipids, TC and TG were higher in patients with the IHD-combined type 1 DM than those in the diabetics without IHD. Thus, IHD exacerbated the DM course. Regardless of the DM type, the HDL C percentage of the total cholesterol was lower in the diabetics with the IHD. The parameter is more instrumental than the absolute TC percentage in the fraction. Calculation of TC/TG coefficients demonstrated changes in the concentrations of TC and TG in the transport forms with the predominance of the latter in patients with the IHD-combined DM of both types.

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EP469

Unmet needs in diabetic neuropathy: A cross sectional analysis from a tertiary care diabetes centre in Sri Lanka

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Background
Diabetic neuropathy, especially distal symmetric polyneuropathy (DSPN), is a common but under-recognized problem among people living with diabetes, particularly in developing countries. Aims: We aimed to describe the clinical characteristics, associated factors, treatment practices, outcomes and impact of DSPN among Sri Lankan adults living with diabetes.
Methods
A cross sectional study was conducted at the Diabetes Clinic of National Hospital of Sri Lanka over 4 consecutive months. Clinic attendees were screened for presence of symptoms and/or signs of DSPN and were invited to participate. Data was collected using an interviewer administered questionnaire which included a SF-36 questionnaire, and through findings from routine end-organ screening.
Results
A total of 201 patients (mean age 60.7 +9.5 years, men 38.8%, mean duration of diabetes 14.4 +8.5 years) were interviewed. Mean HbA1c was 9.3 +2.2% and 87.5% were on metformin. Overall, 92.0% had symptoms of DSPN (numbness 83.6%, pain 64.2%, hyperesthesia 32. 2%), whereas 99.0% had loss of protective sensation (73.9% on 3-point monofilament, 88.6% on increased vibration threshold). 11.9% had foot deformities (hammertoe 10.0%, bunion 2.0%, overlapping toes 1.0%, Charcot 0.5%). While 57.7% had pre-ulcer lesions (toe web infections 50.2%, callosities 13.9%, in-grown toenails 1.5%), 4.5% had active ulcers, and 4.5% had evidence of lower limb amputations. Evidence of diabetic retinopathy was noted only in 41.0% and 19.9% had at least one macrovascular complication. No clinical or demographic factors were associated with DSPN on multivariate logistic regression. Among 129 patients with neuropathic pain, only 35 (27.1%) were given treatment and among them only 8 (24.2%) reported symptom improvement. Painful neuropathy was associated with poor scores in physical functioning, energy level and general health. Despite the presence of diabetic neuropathy, 57.0% were barefoot most of the time.
Conclusions
Feet pain is common among people with DSPN. It remains undertreated and affects QoL. Deformities and toe-web infections are common, placing the feet at high risk of ulceration. There is room to improve foot-care provision and self-management among adults with DSPN.

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EP470

Achilles tendon rupture in an uncontrolled diabetes patient

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Diabetes is one of the risk factors for Achilles tendon rupture. Tendon thickening and impaired collagen organization have been reported in diabetic patients in small studies. In this report, we present the rupture of the Achilles tendon in a female patient with poorly controlled diabetes mellitus and diabetic neuropathy. A 52-years-old woman with a medical history of diabetes treated by intensive insulin therapy, developed pain in the right heel without previous trauma. The patient applied to the hospital because of the inability to walk for the last 5 days. Spontaneous rupture of the right Achilles tendon was diagnosed with MRI. Primary repair of achilles tendon planned. Diabetic ketosis treatment was performed due to preoperative blood sugar being 550 mg/dl and urine ketone positive. Afterwards, the tendon was treated by suture. Chronic hyperglycemia affects the Achilles tendon as well as many organs. Degenerative changes were more common in men and those with peripheral neuropathy. Although the risk of Achilles tendon rupture was more common in those with uncontrolled diabetes and female gender. Systemic approach is important in the follow-up of diabetic patients and heel pain should be evaluated in terms of Achilles tendon rupture, apart from diabetic neuropathy and diabetic foot.

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EP471

Myocardial infarction in young adults with type 1 diabetes mellitus: A case report

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Background
The risk of myocardial infarction among patients with type 1 diabetes is, in addition to traditional cardiovascular disease risk factors, associated with duration of diabetes, reduced glycemic control and renal complications. However, the specific cardiovascular risk predictor models for type 1 diabetes mellitus are subject to many limitations and aggressive macrovascular disease can rarely happen at an early age.
Case Presentation
We report a case of a 22-year-old woman, non-smoker, with a medical history of type 1 diabetes since the age of 4 years old. The glycemic control was not optimal during five years and screening for microvascular complications was negative. Her blood pressure was normal and the lipid profile was within the target with an LDL cholesterol level at 0.6 g/l. She presented an acute chest pain and the electrocardiogram showed a negative T wave in the anterior territory. Echocardiography showed an altered left ventricular ejection fraction of 46% and coronarography revealed an occlusion of the anterior interventricular artery. Angioplasty was successfully performed.
Discussion
The rapidly progressive macrovascular disease observed in this case demonstrates the different degrees of aggressiveness and unpredictable clinical evolution observed in some cases. It also confirms the need for a multi-factorial, early and optimized clinical management regime of type 1 diabetes mellitus.

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EP472

Characteristics of type 2 diabetes in insulin-requiring elderly subjects

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Introduction
Type 2 diabetes, which accounts for more than 90% of all diabetes in the elderly, is a major public health problem. It is associated with high morbidity and mortality, mainly due to complications such as cardiovascular events and renal failure. The objective of our study was to determine the characteristics of type 2 diabetes in insulin-requiring elderly subjects.

Methods
A cross-sectional study on type 2 diabetic insulin dependent elderly recruited from the outpatient endocrinology consultation over a period of 7 months from April 2021 to October 2021.
Results
A total of 282 patients were included in our study with a mean age of 72.33 ± 6.35 years and a sex ratio of 0.9. In association with diabetes, hypertension was the most common chronic disease (71.3%) followed by dyslipidemia (58.9%). The mean duration of diabetes and insulin therapy was 15.89 ± 7 and 7.85 ± 5.5 years, respectively. Only one third of patients were on insulin analogue. The basal double injection regimen was the most prescribed in our population (22.7%). Regular follow-up and self-monitoring of blood glucose were noted in 68.1% and 55% of patients, respectively. Nocturia, hypoglycaemic malaise, unrecognized hypoglycaemia, and severe hypoglycaemia were reported by 59.2%, 69.1%, 23.8%, and 30.5% of patients, respectively. The mean HbA1C level was 9.72% ± 1.81%. Only 17% of our patients had controlled diabetes. Less than a third of the patients (29.8%) had a history of hospitalization for diabetes decompensation, mainly for chronic diabetes imbalance (70.2%). Degenerative complications of diabetes were dominated by microangiopathic complications (83.7%). Diabetic neuropathy accounted for 72% followed by diabetic retinopathy in 57.4% of cases and diabetic nephropathy (17%). Macroangiopathic complications were noted in 45% of cases: the most frequent was arteriopathy obliterating of the lower extremities (27%) followed by myocardial infarction in 23.8% and stroke (12.8%). The diabetic foot was found in 8.5% of patients.
Conclusion
Despite unprecedented advances in insulin therapy and injection means, controlling diabetes in the elderly remains a challenge. Indeed, initiation of insulin therapy in older diabetic patients requires a complete geriatric assessment to identify factors that may complicate diabetes control.

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EP473

Relationship between lipid profile and serum uric acid concentration in patients with type 2 diabetes

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Introduction
hyperuricemia is a marker of cardiovascular risk. The aim of this study was to examine the relationship between lipid profile and serum uric acid concentration in patients with type 2 diabetes (T2D).
Method
A retrospective study including 100 patients followed in the A department of the National Institute of Nutrition in Tunis. Data were collected from patients' medical records. The lipid profile includes low density lipoprotein (LDL), high density lipoprotein (HDL), non high density lipoprotein (non-HDL), triglyceride (TG) and total cholesterol (TC). Hyperuricemia was defined as serum uric acid greater than 6 mg/dl (360 µmol/l).
Results
The mean age of patients was 56.75 ± 12 years ,48% were men and 52% were women. The average duration of diabetes was 8.27 ± 6 years. The mean body mass index (BMI) was 29.55 ± 4.33 kg/m^2. Almost one third of the patients (29%) had hyperuricemia (with no clinical manifestations of gout) and 64.5% had dyslipidemia. We found a positive and statistically significant correlation between TG and uric acid level (r = 0.45, P0.002). Non-HDL cholesterol was positively correlated with uric acid levels and trend to significance (r = 0.28, P0.052). There was no correlation between LDL, HDL and uric acid concentration.
Conclusion
The results of our study illustrate the strong association between uric acid increase and lipid disorder in patients with T2D suggesting a crucial role of uric acid in the regulation of dyslipidemia.

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EP474

Assessment of diabetic patients' knowledge of the diabetic foot

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Introduction
Trophic disorders of the diabetic foot and their complications represent a major public health problem. Treatment must be accompanied by quality therapeutic education to allow patients to self-manage their disease. The objective of this work is to evaluate, with the help of a questionnaire, the knowledge of diabetic patients on the diabetic foot.
Materials and Methods
We conducted a descriptive, cross-sectional study among 50 diabetic patients hospitalized in ward A, at the National Institute of Nutrition in Tunis.
Results
The average age of our patients was 52 ± 12 years with a M/F sex ratio of 0.22. The majority of patients were type 2 diabetics (n = 34). The average age of diabetes was 12.5 ± 7 years. During the clinical examination of the foot, plantar hyperkeratosis was the most noted manifestation with a frequency of 72%. It was noted that 86% of the patients had never attended a therapeutic education session for diabetic foot and 48% of the patients had no idea about its mechanisms and favoring factors. Regular foot inspection was present in only 28% of patients, while 26% were unaware of the clinical manifestations and 30% did not cite any means of prevention. On the other hand, 92% of our patients knew that amputation was the main risk of the diabetic foot.
Conclusion
Therapeutic education of patients regarding the diabetic foot is crucial. Nevertheless, educational deficiencies persist, highlighting the need for a structured program involving the entire health care team.

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EP475

Hospital investigation of hypoglycemia in type 1 diabetics: About 28 cases

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Introduction
Hypoglycemia is a major obstacle to glycemic control in type 1 diabetics. Approximately two episodes of symptomatic hypoglycemia occur weekly in type 1 diabetic and this risk increases with the duration of diabetes and the strict control[1]. The aim of this study was to identify the most frequent etiologies of hypoglycemia in hospitalized type 1 diabetic patients.
Patients and Methods
This is a retrospective descriptive study that involved 28 type 1 diabetic patients hospitalized for hypoglycemia in the endocrinology department of the Taher Sfar University Hospital of Mahdia between 2011 and 2022.
Results
The average age of our patients was of 34.44 ± 13.88 years. The patients were divided into 6 men and 22 women. The average duration of diabetes was of 11.7 ± 7.45 years. The mean glycated hemoglobin in our patients was of 9.46% ± 2.68. The average frequency of hypoglycemia was 3 episodes per week. Severe hypoglycemia was present in ten cases. Several interrelated factors were often incriminated in the same patient. Hypoglycemia was attributed to poor education in 13 patients: 6 cases of insulin dose error, 6 cases of dietary error, 6 cases of injection in lipodystrophic areas. Two cases of hypoglycemia were attributed to severe renal failure. Hypoglycemia secondary to Addison's disease was diagnosed in 15 patients. A context of a malabsorption syndrome due to celiac disease has been demonstrated in three patients. Fake hypoglycemia was the cause of hypoglycemia in one patient.
Discussion and Conclusion
Hypoglycemia is a dread for any caregiver because of its neurocognitive impact on the quality of life and carbohydrate balance of type 1 diabetics. Rigorous etiological research is needed, requiring sometimes hospitalization and treatment reevaluation. In the literature, the occurrence of Addison's disease in type 1 diabetics is rare with a prevalence of 1.2%[2]. The explanation of the higher prevalence of Addison's disease in our population need to be explored.
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EP476

Bezold abscess in diabetics: A case report

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Introduction
Benzold abscess remains rare, and its occurrence implies immunosuppression, particularly within unbalanced diabetes.
Methods and Results
Observation of a 76-year-old patient, diabetic for 29 years, on metformin, admitted for CMO of the right ear, complicated by Bezold's abscess. The interrogation revealed purulent otorrhea hypoacusis. The clinical examination revealed hyperglycemia,a swelling of the sternocleidomastoid, responsible for a torticollis. MRI of the rocks: abscessed and fistulated right cholesteatomatous otitis in the sternocleido-mastoid muscle. The biological tests showed an inflammatoire profil. Management: Insulin therapy and oral antidiabetics, drainage.
Discussion
Bezold's abscess is a rare extra-cranial complication of CMT occurring in immunosuppressive conditions such as chronic hyperglycemia in diabetes. It requires a CT scan or better an MRI for diagnosis. While the management is essentially based on an adapted antibiotics associated most often with surgical drainage.
Conclusion
Diabetes is an immunosuppressive factor exposing patients to an increased risk of infections such as abscess. Early, efficient and multidisciplinary management is required management to improve the prognosis.
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EP477

Digital necrosis in a diabetic patient with probable Leo berger's arteritis

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Introduction
Digital necrosis of the upper limbs is the final and often the only clinical manifestation of a of a distal arterial or microcirculatory pathology of the MS. The approach to The approach to this condition is very different, hence the particularity of our observation which highlights the severity of vascular lesions found in diabetic patients.
Observation
This is a 58 year old diabetic patient on mixtard 30: 16-00-08 ui; schizophrenia; on classic neuroleptic drugs; alcoholic and chronic smoker at Interrogation: Poorly monitored diabetes; Incoherent proposalsincoherent;an exacerbation of SPUPD;clinical examination: Patient conscious, cachectic, BMI 15 kg/m^2; Radial pulse weakly perceived bilaterally; Neuropathic feet; Thyroid not paLpable;On workup: Nfs: normal; CRP: negative;Ionogram: normal; Liver workup: normal;-AFP:8.19; CA19-9=1.1; total PSA =2; free PSA=0.338; serology: negative,echodopler of the MS: requested, the therapeutic management was based on:Optimization of his insulin regimen +local treatment of digital lesion.
Discussion and Conclusion
Digital necrosis and ulceration of the upper limb have various causes (vascular and metabolic, mechanical, toxic, etc.) and are often of polyfactorial origin. The positive diagnosis of a digital necrosis of the upper limbs is easy and represents only the visible face of a microcirculatory arterial pathology of the upper limb dominated by leo-burger type arteritis as in the case of our patient.

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EP478

Diabetic Nephropathy

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Introduction
Nowadays, Diabetic nephropathy (DN) has become one of the leading causes of end-stage kidney disease.
Aim
The aim of our study was to determine the prevalence of diabetic nephropathy and to investigate its association with other comorbidities associated with diabetes.
Methods
A retrospective descriptive study was performed on 369 diabetic patients hospitalized in the c nutrition and metabolic diseases department. The definition as well as the different stages of diabetic nephropathy have been retained referring to the recommendations of the American Diabetes Association (ADA) of 2022.
Results
The median age of patients was 56.43 $\pm$15.7 years old. The majority of patients in our study has type 2 diabetes (65.6%).The average duration of development of diabetes is 11 years. The prevalence of DN was 42.8% (29.1% stage 1; 8.2% stage 3; 2.1% stage 2; 2.5% stage 4 and 0.9% stage 5). Among them 31.3% has microalbuminuria and 11.5% has macroalbuminuria. High blood pressure is noted in 58.3% of patients with DN. High fasting blood glucose values as well as glycated hemoglobin outside the targets were noted in 78% of patients with DN. In our study a significant correlation was found between DN and diabetic retinopathy ($P<10$-3) , dyslipidemia ($P=0.004$) and the duration of diabetes ($P<10$-3). Nevertheless, there were no significant differences in age($P=0.283$) sex ($P=0.277$) and type of diabetes ($P=0.725$) between those with and without DN.
Conclusion
The prevention of the Diabetes kidney disease is a global challenge based on early detection to limit the progression to terminal kidney disease.

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EP479

A Rare Complication of Diabetes: Hemiballism Syndrome Associated with Non-ketotic Hyperglycemia

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Introduction
Hemiballism is a rare hyperkinetic movement disorder characterized by involuntary, violent, coarse and wide-amplitude movements involving the ipsilateral arm and leg. Here, we aimed to present a case diagnosed as hemiballism due to non-ketotic hyperglycemia.
Case Report
A 60-year-old female patient presented to the emergency department with involuntary movements in the right half of the trunk for 10 days. It was a large amplitude proximal extremity movement in the right arm and also occurred in the right lower extremity. Movements did not continue during the night's sleep. On physical examination, she was conscious and well oriented to time and place. Hemodynamics and vital signs were stable. There was no sign of facial paralysis. Osteotendinous reflexes were symmetrical. Cranial nerves were intact. There were no other accompanying physical examination findings. She had type 2 diabetes for 10 years. She was using gliclazide 30 mg and linagliptin 5 mg, but she did not have regular doctor checks and did not measure blood glucose. She had no history of alcohol or substance abuse. Laboratory results showed a high plasma glucose of 540 mg/dl and a serum osmolarity of 302 mOsm/kg. The patient's kidney and liver functions were normal and there was no accompanying serious electrolyte imbalance. There was no finding compatible with metabolic acidosis in venous blood gas, there was no ketone positivity in urinalysis, and glucosuria was present. No signs of intracranial hemorrhage or ischemia were detected in the brain computerized tomography (CT) imaging, and there was an increase in asymmetric density at the right putamen compared to the left. Similarly, there was hyperintensity on T1-weighted sequences at the right putamen in brain

magnetic resonance imaging (MRI). As a result of clinical, laboratory and radiological evaluations, the patient was accepted as non-ketotic hyperglycemia-associated hemibalism syndrome. The patient was first hydrated, crystallized insulin infusion was started with close blood glucose monitoring, and then intensive insulin therapy was started. When plasma glucose began to improve, involuntary extremity movements also decreased. At 3-month follow-up, both normoglycemia and hemiballism were almost completely resolved.
Conclusion
Non-ketotic hyperglycemia-associated hemiballism syndrome is a rare initial manifestation of diabetes and is usually seen in elderly diabetic patients with poor glycemic control. It should be kept in mind that hemiballism may be the first sign of undiagnosed diabetes, and this rare neurological complication should be recognized as it is easily resolved with hyperglycemia treatment.

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EP480

Clinical aspect and diagnosis of osteomyelitis in diabetic foot

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Introduction
Diabetic foot osteomyelitis is a frequent complication of a preexisting infected foot wound. It is mostly the consequence of a soft tissue infection that spreads into the bone thus increasing the risk of amputation and the burden of foot care. The aim of this work is to describe the clinical and therapeutic aspect of diabetic foot osteomyelitis in our department.
Patients and Methods
It's a retrospective and descriptive study conducted in our department, between January 2008 and January 2021, including all diabetic patients with foot osteomyelitis. Statistical analysis was performed using SPSS software.
Results
A total of 127 patients with a mean age of 57 years old were included. Male patients represented 61.3% of patients. Most of them were type 2 diabetics (84%) with a mean duration of 11.5 years and an average HbA1c of 11.3%. The diagnosis was essentially clinical, based on the chronic evolution of the ulcer, the presence of positive probe-to-bone test and the sausage-like toes. X-ray imaging often found erosion of cortical bone, osteolysis and in some cases bone sequestrations. Serum inflammatory markers as white blood cells (WBC), C-reactive protein and procalcitonin (PCT) were usually high when associated with soft-tissue or systemic infection. The treatment consisted of antibiotic therapy with an average duration of 9 weeks. Off-loading, perfect glycemic control and thromboembolic prevention were indicated in all patients. Among the cases, 9% were referred to surgical department for surgical management of necrosis and collections.
Conclusion
Osteiteomyelitis is an infection that can complicate diabetic foot ulcers. Early and optimal diagnosis and management limit the risk of unfavorable evolution, thus minimizing the risk of surgery and amputation.

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EP481

Perception of the risk of becoming type 2 diabetic in patients with gestational diabetes

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Introduction
Gestational diabetes is a state of glucose intolerance, regardless of its severity, discovered during pregnancy in a woman not known to have diabetes before pregnancy. It is associated with a risk of recurrence in subsequent pregnancies and progression to type 2 diabetes.The objective of this work was to evaluate the perception by parturients of the risk of recurrence and type 2 diabetes, to evaluate their knowledge of preventive measures and their adherence to these measures, and thus, to light on the value of monitoring these patients even after delivery.
Materials and Methods
Prospective descriptive study conducted at the Department of Endocrinology-Diabetology of the UHC Ibn Rochd – Casablanca, in patients followed for gestational diabetes, and having answered a questionnaire that we established in order to evaluate their knowledge in particular concerning the risk of progression to T2D and the benefit of follow-up.
Result
The average age of our parturients was 31 years (22-45), with an average gestational age of 28SA, the average body mass index (BMI) before pregnancy was 29.3 kg/m^2, with an average weight of 11.3 kg (9-15) during pregnancy. Treatment by lifestyle and dietary rules was sufficient in 68.7% of our parturients and 40.8% had a family history of type 2 diabetes. The majority considered themselves at high risk of becoming diabetic (65.4%), but 38.2% had no not changed their diet, and 85.5% had not changed their physical activity. Among our patients, 15% were postpartum, and all were aware of the value of follow-up, but none had maintained the lifestyle and dietary rules after childbirth. The perception of the risk of developing type 2 diabetes was not significantly influenced by gestational age at the discovery of diabetes, nor by previous BMI or weight gain during pregnancy. However, patients treated with insulin, as well as those with a family history of type 2 diabetes, considered themselves at greater risk of becoming diabetic ($P<0.01$).
Conclusion
Gestational diabetes is a risk factor for the onset of type 2 diabetes. Parturients are often unaware of this risk, and lost sight after the delivery. Hence the interest of highlighting these data when educating parturients with gestational diabetes, in order to make them aware of this risk, and thus, encourage them to pursue a healthy lifestyle with regular follow-up, even after childbirth.

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EP482

Factors affecting the severity of diabetic foot ulcer

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Introduction
Diabetic foot is a public health problem that affects the quality of life of diabetic patients. The severity of diabetic foot ulcer causes complications that are not only costly but can lead to amputation. The objective of this work is to study the factors related to the severity of diabetic foot ulcers.
Material and Methods
It's a retrospective study from January 2020 to May 2022 involving patients treated in the endocrinology department for diabetic feet. The severity of the lesions was evaluated by the Wagner classification. The analysis was performed using SPSS 21 software.
Results
The total of patients was 175, with an average age of 56 years, of which 64% were male and 36% female. Type 2 diabetic patients represented 87.4% of patients. The average duration of diabetes was 14.7 years. Most of patients were unbalanced with an average HbA1c of 14.7%. About degenerative complications, 70.3% had diabetic microangiopathy and peripheral arterial disease was present in 53.1% of cases. Among these patients, 9.7% had a history of amputation. Concerning ulcers, 44% had grade 1 ulcers of the Wagner classification, 48.6% grade 2 ulcers and only 7.4% grade 3 ulcers. The factors associated with the severity of the lesions were the duration of the diabetes ($P=0.009$), glycemic imbalance ($P=0.001$) association with arteriopathy ($P=0.001$), history of amputation ($P=0.003$) and the existence of Charcot's foot ($P=0.001$.
Conclusion
The study of factors involved in the severity of diabetic foot lesions will allow the implementation of preventive measures and greater vigilance in patients at risk carrying these factors.

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EP483

Diabetic foot and vascular damage: About 102 cases

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Introduction
Diabetes promotes the development of arterial damage. Peripheral arterial disease is a classic localization of macroangiopathy, serious in its evolution; it constitutes a major risk factor for the occurrence of foot lesions in diabetics.

Goal of the Study
The aim of our study is to analyze the vascular profile of diabetic patients hospitalized for diabetic foot.
Patients and Methods
Descriptive retrospective study taking place over a period of 3 years, including 102 diabetics hospitalized in the endocrinology-diabetology department of the CHU Ibn Rochd for foot lesions.
Results
The average age of our patients was 57.5 years, with a clear male predominance of 62.7%, type 2 diabetes predominated in 85.2% of cases with a duration of evolution greater than 10 years in 74.5% and an average of HbA1c of 10%. The major risk factors for atherosclerosis found in our patients were dyslipidemia in 48% of cases, hypertension in 46%, obesity in 36.2%, smoking in 16.6% and physical inactivity in 60.7% of cases. Target organ damage was found in 56.8% of our patients, of whom 49% had diabetic retinopathy, 27.4% had diabetic nephropathy and 45% had peripheral neuropathy. 12.7% of our patients had a history of amputation. 68.6% of our patients were classified at very high cardiovascular risk. The foot lesions found were: MPP in 35% of cases, arteritic ulcer in 29.4% of cases, dermohypodermitis in 24.5% and osteitis in 23.5%. The ankle brachial index was pathological in 68.8% of patients, where 50% had an ABI <0.9 and 18.6% had an ABI >3. Doppler ultrasound objectified PAD in 88.2% of patients, arterial stenosis was found in 24.5% of cases where it was bilateral in 6.9%, atheromatous overload was present in 48.5% of patients and mediacalcosis in 15.9%. Doppler returned normal in 11.7% of patients. The evolution was marked by infection in 32.5% of patients and necrosis in 1.9% of patients. The mean healing time was 77 days.
Conclusion
The peripheral arterial disease is a serious complication of diabetes and the main factor of amputation. Prevention through the fight against cardiovascular risk factors is the basis of treatment.

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EP484

Prevalence of autoimmune diseases in patients with type 1 diabetes

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Introduction
Type 1 diabetes (T1D) is frequently associated with other autoimmune diseases The Aim of the study is to determine the prevalence of autoimmune diseases (AID) that may be associated with type 1 diabetes and to study the particularities of this association.
Patients and Methods
this was a retrospective study including 251 patients with type 1 diabetes followed in the diabetology, endocrinology department of the IBN Rochd hospital center in Casablanca. Clinical and paraclinical data were recorded for all patients.
Results
The study population was composed of 116 women (46.2%) and 135 men (53.8%). The average age was 25.2 years and the average duration of diabetes was 10.82 years. Autoimmune diseases were found in 32 patients or 12.74%: 21 women and 11 men. Autoimmune dysthyroidism topped the list with 8 cases of Graves' disease and 6 cases of Hashimoto's thyroiditis, followed by 6 cases of Addison's disease, 5 cases of psoriasis, 4 cases of celiac disease and 3 cases of vitiligo. Patients with associated AID were older (29.4 vs 24.6 years; $P=0.005$) and had longer diabetes duration (12.55 years vs 9.57 years, $P= 0.001$) and a higher prevalence of microangiopathy (41.9% vs 22.27%) ($P=0.005$). The prevalence of macroangiopathic complications was comparable between patients with and without AID ($P=0.2$). On the other hand, the cardiovascular risk was significantly higher in patients with other autoimmune diseases ($P=0.001$).
Conclusion
The coexistence of autoimmune diseases in patients with type 1 diabetes is not uncommon. According to our results, this association is characterized by an increase in microangiopathic complications and cardiovascular risk, which further encourages them to be detected and treated at the discovery of diabetes.

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EP485

Diagnosis and management of acute Charcot foot

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Introduction
Diabetic osteoarthropathy or Charcot's foot is a serious complication of diabetes whose early diagnosis is complex and often delayed. It manifests itself in the acute phase by localized inflammation of the foot or ankle, and in the absence of discharge, it leads to severe bone damage. Hence the need for better knowledge and early and adequate treatment.
Goal of the Study
The aim of our study is to describe a cohort of diabetic patients followed for acute Charcot foot.
Patients and Methods
Retrospective study over 3 years taking place from May 2019 to May 2022 at the CHU Ibn rochd. 28 records of patients followed for Charcot's foot were collected, including 6 received in the acute phase. We describe the 6 patients followed for acute Charcot's foot secondarily confirmed by imaging. Stabilization of Charcot's foot was defined by the clinical disappearance of inflammatory signs.
Results
The average age of our patients was 51 years old, with a clear male predominance of 5/1 and an average BMI of 25.6 kg/m^2. Type 2 diabetes predominated in 66.6% with an average duration of evolution of 14 years, the mean HbA1c was 9.7%. The injury was in the right foot in 83.3% of cases. The clinical elements reported were swelling in 100% of cases, warmth in 83.3% of cases, redness in 66.6% of cases, deformities were described in 33.3% of cases. The main triggering factors were unsuitable footwear in 50% of cases and trauma in 33.3% of cases. The mean time to diagnosis was 50 days. All the patients benefited during the initial phase from a strict discharge by circular fenestrated cast in 83.3% and by thermoformable splint in 16.6% of the cases then of a relay by orthopedic shoe in 100% of the cases. One patient received medical treatment with bisphosphonates. Stabilization was obtained in 83.3% of patients with an average delay of 274 days.
Conclusion
Acute Charcot's foot is a rare but severe complication, difficult to identify, it is often underdiagnosed, causing delays in management and compromising the functional prognosis of the diabetic patient.

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EP486

The prevalence and risk factors of peripheral arterial disease in diabetics

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Introduction
Peripheral arterial disease (PAD) is a classic localization of macroangiopathy in diabetics. It is a major risk factor for amputation.
Goal of the Study
know the prevalence and analyze the risk factors associated with peripheral arterial disease.
Patients and Method
Descriptive and analytical retrospective study conducted in the department of endocrinology and metabolic diseases of the CHU Ibn Rochd, where 544 asymptomatic diabetic patients were screened for peripheral arterial disease. PAD was defined by an ABI measurement less than 0.9 or greater than 1.3.
Results
A total of 544 patients were included in our study, 65.6% of whom were women. The average age of our patients was 51.2 years (15-89). Type 2 diabetes predominated in 80.5% of cases with an average duration of evolution of 10.6 years and an average HbA1c of 10.1%. The prevalence of PAD was 21.7%. The risk factors significantly associated with PAD were: advanced age ($P=0.001$), hypertension ($P=0.002$), dyslipidemia ($P=0.002$), physical inactivity ($P=0.002$), coronary artery disease ($P=0.001$), a history of stroke ($P=0.027$), the presence of micro albuminuria ($P=0.001$), retinopathy ($P=0.001$) and diabetic neuropathy ($P=0.000$). On the other hand, neither tobacco nor obesity was linked to PAD.
Conclusion
The prevalence of PAD is high in diabetics. These results encourage systematic screening and rigorous follow-up of high-risk patients and to include control of cardiovascular risk factors and glycemic control in management strategies.

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EP487

Clinical and paraclinical profile of patients followed for idiopathic hirsutism: About 30 cases

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Introduction
Hirsutism is a frequent reason for consultation, it is defined by the presence of terminal hair with male distribution in women, it is however essential to determine the cause, since it can reveal a serious underlying pathology and as it may be due to a benign cause see idiopathic in some cases. Idiopathic hirsutism is second in line to polycystic ovary syndrome in the etiological search for hirsutism. The objective of this study is to describe the clinical and paraclinical aspects of idiopathic hirsutism in patients.
Patients and Methods
This is a retrospective and descriptive study of 30 patients followed for idiopathic hirsutism at the Endocrinology-Diabetology-Nutrition Department of the Mohammed VI University Hospital center in Oujda. The collected data were analyzed by SPSS-version-21 software. All patients benefited from a biological exploration of the adrenal gland (synacthene test, 24-hour urinary cortisol level), and a pelvic ultrasound.
Results
Idiopathic hirsutism represents only 20% of the causes of hirsutism in our series, the average age of our patients was 24.9 ± 5.1 years [16-35 years]. Hirsutism appeared during puberty in 33.3% of cases and after puberty in 50% of cases, it was mild in 33.3%, moderate in 43.3% and severe in 23.3% of cases, with an average Ferriman and Gallwey score of 17.9 ± 5.2. However, all the patients in our series did not have menstrual cycle disorders. Concerning the other minor signs of hyperandrogenism, acne and seborrhea were found in 56.7% and 20% of cases respectively. Overweight was reported in 33.3% and obesity in 13.4% of patients with 3 cases of metabolic syndrome (10%). Biological exploration showed a mean testosteronemia level of 0.47 ± 0.24 ng/ml. Dyslipidemia was observed in 13.3% of cases, of which hypoHDLemia was the most frequent lipid anomaly (40%) and 27% of carbohydrate tolerance disorders.
Discussion and Conclusion
The etiologic investigation of hirsutism requires careful exploration for an accurate diagnosis and to rule out any adrenal or ovarian causes before retaining the diagnosis of idiopathic hirsutism and thus to guide the therapeutic management. This study shows that metabolic disturbances have been demonstrated in these patients, but their prevalence remains low, which is consistent with the data reported in the literature. Other studies on a larger number of patients should be carried out to study insulin resistance in women followed for idiopathic hirsutism in order to establish new and more effective therapeutic strategies.

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EP488

Nutrition and body changes during the menstrual cycle in women of childbearing age

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Objective
Changes in mood, appetite, dietary intakes and physic during a menstrual cycle has been controversial in studies. The aim of this study is to determine the nutritional behavior and body changes during the menstrual cycle in women of childbearing age by comparing dietary records and anthropometric measurements in three phases of menstrual cycle.
Method
This prospective study included 34 healthy regularly menstruating women aged 20-39 years in April-May 2022. Women were followed during one menstrual cycle, three face to face interviews were conducted at three phases during a cycle. The phases of menstrual cycle of women was determined as secretory, menstruation and proliferative by a obstetrician. The data form consists of questions on sociodemographic characteristics such as age, marital status, income, education level and the second part consist of questions about nutritional behaviors at the three phases of menstrual cycle. All anthropometric measurements were taken at the three phases of menstrual cycle via bioelectrical impedance analysis. Three day food records were taken in three phases of menstrual cycle.
Result
There were not any changes of anthropometric measurements during the menstrual cycle. Women had significant changes between phases on experiencing anxiety, tiredness, irritability, depressive thinking, pain, swelling and edema, sweet craving and appetite increase ($P < 0.05$). These mood and appetite changes reduced especially in proliferative phase. In menstruation phase, an increase in fiber, vitamin B1, vitamin B9, vitamin C, potassium, magnesium, phosphorus, iron and zinc intake compare to secretory phase was detected. Although energy, carbohydrates and protein intakes increased in menstruation phase, and fat intake was higher in proliferative phase, these changes were not statistically significant.
Conclusion
Women who participated to this study had changes in moods and appetite but not in anthropometric measurements during a menstrual cycle. Understanding these changes is of great importance for women's and menstrual health. Keywords: Dietary Intake; Menstrual cycle; Women; Weight

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EP489

Obesity in 3q29 microduplication syndrome: An inherited case report and literature review

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Background
3q29 microduplication syndrome is a very uncommon genetic disorder with fewer than 40 cases reported, although the wide and heterogenous clinical features make this syndrome hard to diagnose. This syndrome is clinically milder than the 3q29 microdeletion syndrome, which contributes to the high rate of underdiagnosed cases that may exist. Patients affected with this syndrome have a complex phenotype, with non-specific clinical features such as autism spectrum disorders, psychiatric comorbidities, intellectual disability, overweight and craniofacial dysmorphisms, among others. Apart from the previously described ones, obesity, muscular hypotonia, speech delay, microcephaly and ventricular defects are often reported.
Objective
We report the clinical case of a 15-year-old male with a 3q29 microduplication syndrome diagnosed while ruling out a Prader-Willi syndrome. We summarize the literature, and compare our patient phenotype with the previously reported cases.
Methods
Genome-wide copy number analysis was carried out using single-nucleotide polymorphism microarray. The study revealed a 3q29 microduplication with a 1.5 Mb length, affecting DLG1 gene.
Results
A 15-year-old male who was sent to the Endocrinology and Nutrition department due to his overweight, in order to discard secondary causes of obesity and offer treatment. The main medical history of the patient included an early diagnosis of autism with low IQ (<70) in cognitive tests, dysfunctional personality with obsessive-compulsive tendencies and a mixed anxious-depressive syndrome. The patient referred an important and progressive weight gain since he was 8 years old with bad dietetic habits. Physical examination was unremarkable. Low-set ears were the unique facial dysmorphism present in the patient. His height was 1.79 m (85th centile), weight was 117.7 kg (99th centile) and BMI was 36.7 kg/m^2 (99th centile). The genetic study revealed a 3q29 microduplication affecting DLG1 gene, which could potentially explain the patient's clinical features. Same mutation was found in the mother. 3q29 microduplication phenotype is widely variable. There are very few clinical cases series published in medical literature, but as reported in some reviews obesity is found in 50% of the cases described.
Conclusions
Our patient showed moderate intellectual disability, autism, psychiatric disorders, obesity and chronic constipation as main feautres of this syndrome. The management of patients affected with this syndrome depends on the moment of diagnosis but includes ophthalmological, cardiac and auditory evaluation, with psychiatric/psychological support when needed. Genetic counselling should be made.

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EP490

Autoimmune polyglandular syndrome type 3: A case report

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Introduction
Autoimmune polyglandular syndromes are characterized by the coexistence of two or more autoimmune endocrine diseases, however, coexistence of various non-endocrine disorders is also possible. Autoimmune polyglandular syndrome type 3 (APS-3), is the co-occurrence of autoimmune thyroid disease (AITD) with diabetes type 1, but without Addison disease. The coincidence of AITD and latent autoimmune diabetes of the adult (LADA) is relatively less described.
Case Report
We present the case of a 50-year-old female patient with APS-3 associated with Hashimoto's thyroiditis, latent autoimmune diabetes of adult and vitiligo. A 50-year old woman presented to the clinic with a few months history of complaints: Increased thirst, frequent urination, weight loss. Hyperglycemia was revealed. HbA1c - 12.7%. C peptide was very low. Glutamic acid decarboxylase antibodies (GAD 65-Ab) were measured- >250 IE/ml ($n<10$); Latent autoimmune diabetes of the adult (LADA) was diagnosed and insulin therapy was started. Personal history revealed vitiligo within the past 5 years. With additional studies patient was also diagnosed with Hashimoto's thyroiditis: TSH, FT4- within normal reference ranges, the level of anti-TPO - 1685 (N 0-5.61 IU/ml), anti-TG- also elevated- 6.76 (N 0-4.11 IU/ml). Dyslipidemia was also diagnosed. Currently, the patient is on regular follow-up. LADA and dyslipidemia are well controlled; She still remains euthyroid.
Conclusion
APSs are rare conditions characterized by autoimmune disorder of multiple endocrine glands, with or without autoimmune disease of non-endocrine organs. The hypothesis of APS should be raised in patients with one autoimmune endocrine disease.

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EP491

Pedal acrometastasis secondary to transitional cell carcinoma of the bladder masquerading as Charcot arthropathy in a patient with type 2 diabetes

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Background
Metastatic disease is common in bone, with the majority occurring in the spine, pelvis, and long bones such as the femur and humerus. Acrometastasis, a term used to describe malignant spread distal to the elbow and knee, is a pattern less commonly seen. Its rarity often leads to delayed diagnosis; the condition may be confused with more common conditions such as inflammatory arthritis and Charcot neuroarthropathy, the latter especially in particular in patients with diabetes mellitus. This can lead to poor patient outcomes, with a serious impact on survival.
Case Presentation
An 80-year-old lady with type 2 diabetes mellitus and a history of previous non-invasive papillary carcinoma of the bladder, previously documented to be in remission, presented to her general practitioner with left foot pain following trauma. Initial radiographs were normal, prompting a diagnosis of a simple sprain. 3 months later, the patient was referred to the orthopaedic team due to worsening pain. Examination revealed erythema and swelling, but pulses were present and no neuropathy was detected. Repeat x-rays revealed lytic lesions in the talus and navicular bones. MRI confirmed a lytic and proliferative defect and was reported as likely acute Charcot arthropathy with superimposed infection, leading to subsequent referral to the diabetes team. Charcot arthropathy was also considered the most probable diagnosis when imaging was reviewed by specialists in two separate multidisciplinary team meetings. Bone biopsy was recommended as part of the further work-up given the patient's history; this demonstrated sheets of malignant tumour cells in keeping with metastatic transitional cell carcinoma. The patient was subsequently diagnosed with pedal acrometastasis from her existing malignancy, an infrequently described entity within the medical literature.
Discussion
This case identifies and draws awareness to a rare complication of malignancy, as well as highlights the importance of maintaining an open differential diagnosis in suspected Charcot arthropathy; a complication of diabetes that is often misdiagnosed, impacting patient morbidity and mortality[1]. Clinicians should maintain a low threshold for ordering a biopsy to permit the histological exclusion of other diagnoses, particularly in individuals with known malignancy; this patient's case emphasises the potential for diagnostic uncertainty even with advanced imaging and expert interpretation.
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EP492

Severe Hypoglycemia after Levofloxacin Use: A case report

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Introduction
Levofloxacin is a fluoroquinolone group antimicrobial agent widely used in the treatment of community- and hospital-acquired infections. There have been reports of glucose homeostasis abnormality associated with the use of fluoroquinolones including gatifloxacin, levofloxacin and ciprofloxacin. This report presents the case of a patient with type 2 diabetes mellitus who developed severe hypoglycemia following oral levofloxacin use.
Case
A 77-year-old female patient was being followed for chronic atrial fibrillation, heart failure, asthma, hypothyroidism, and type 2 diabetes mellitus. For treatment of her diabetes, she was receiving intensive insulin therapy (a total of 110 units daily) and metformin, sitagliptin and empagliflozin. Two months ago, the patient was treated in an external center for COVID pneumonia, and was discharged on oral levofloxacin 500 mg/day two days before admission to our center. Following discharge, the patient developed confusion at home, and her blood glucose level was found to be 52 mg/dl, upon which she was admitted to our clinic for further investigations. We discontinued the antidiabetic medications. Differential diagnosis was performed to identify the causes of hypoglycemia, which ruled out adrenal insufficiency. The detailed history of the patient revealed that her complaints started on the second day of levofloxacin use. Levofloxacin was thought to be the possible cause of hypoglycemia and was discontinued. During the first three days, she had normal blood glucose levels. Starting from day four, her blood glucose started to increase up to 300 mg/dl. She was initially started on basal insulin; basal insulin was gradually increased and insulin aspart boluses were added. The patient was stabilized with basal bolus insulin therapy and was not given oral antidiabetics due to her GFR and serum creatinine levels. Her overall condition remained stable and her complaints regressed. She was discharged with a total daily insulin dose of 82 units (3×14 units of insulin aspart, 40 units of U300 insulin glargine).
Discussion
Levofloxacin-induced hypoglycemia is a rare complication, and although few cases have been reported in previous studies, some patients were reported to have severe and fatal hypoglycemia. Although levofloxacin is widely used, there is limited awareness of its possible hypoglycemic effects. Increased awareness of this side effect of levofloxacin may reduce the mortality and morbidity rates associated with the rare but life-threatening side effect of this widely used antibiotic. When selecting drugs for comorbidities in diabetic patients, it is crucial to consider potential effects of medications on glucose metabolism.

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EP493

Differential performance in SIMBA simulation-based training sessions between healthcare professionals from low-and-middle income and high income countries suggests targeted education is needed to reduce the gap

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Introduction
The global migration of healthcare professionals has enabled those trained in low-and-middle income countries (LMICs) to move and work in high-income countries (HICs) and vice-versa. While medical licensing exams in HICs are designed to assess competency of the immigrating HCPs, there is limited literature on the differences in approach to manage clinical cases between those from LMIC and HIC. Simulation via Instant Messaging – Birmingham Advance (SIMBA) is a simulation-based training model using real-life clinical cases simulated via WhatsApp and Zoom. Participants from all over the world have been attending the sessions since its inception in 2020. In this study, we investigated if there was a difference in performance during SIMBA between participants depending on their country of residence.
Method
All participants who attended and completed both pre- and post-SIMBA surveys in 17 SIMBA sessions from 2020 to 2022 were included in this study. Participants were grouped into those from LMICs and HICs according to their country of residence based on the 2022 World Bank report. Participants' performance was assessed using the Global Rating Scale (GRS) adapted for each session, which scored the participant on a scale of 1 (poor) to 5 (excellent) in 6 domains: History Taking, Physical Examination, Investigations, Result Interpretation, Clinical Judgement, and Management. The mean GRS domain scores were calculated using multiple linear regression models, adjusting for sex, country, training, and number of WhatsApp messages. Mean difference between performance scores was calculated using a paired *t*-test.
Results
A total 281 participants ((HICs – 191 (67.9%), LMICs – 90 (32.0%)) from 49 countries ((HICs – 18(36.7%), LMICs – 31(63.2%)) were included in this analysis. Participants from LMICs scored lower in History Taking (LMICs: 3.5 vs HICs: 3.8; $P=0.0117$), Investigations (LMICs: 3.1 vs HICs: 3.6; $P=<0.0001$), Clinical Judgement (LMICs: 2.9 vs HICs: 3.4; $p=<0.0001$), and Management (LMICs: 2.3 vs HICs: 2.9; $P=<0.0001$). The performance was similar for participants across all countries in Physical Examination (LMICs: 3.5 vs HICs: 3.6; $P=0.2335$) and Result Interpretation (LMICs: 2.6 vs HICs: 2.8; $P=0.3264$).
Conclusion
There is a difference in performance of solving clinical cases between participants from LMICs and HICs which may reflect the difference in clinical training in their local region. Future research whether serial simulation-based learning can reduce this difference is currently underway.

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EP494

Standard deviation

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We studied regarding simplifying standard deviation (SD) and useful metrics for achieving target SD. In a cross-sectional study, we analyzed 24-h glucose levels measured using continuous glucose monitor (CGM) [iPro2] in 150 patients with type 2 diabetes. We analyzed 51 time in range (TIR) (reference ranges: mean glucose level (M)±20, M±21 … M±69, M±70 mg/dl [we referred to the underlined numbers as "Margin"]). We analyzed optimal cutoff values of TIR to predict SD below target, corresponding to 51 TIR × 26 target SD (25, 26 … 49, 50 mg/dl), using receiver operating characteristic analysis. Of the 51 reference ranges, the reference range for which TIR had the largest AUC for each target SD was referred to as "optimal reference range 1". We arranged the patients in ascending order of SD, ranking from 1 to 150. Consecutive 110 patients were selected 41 times while shifting one by one (from "1–110" to "41–150": 41 groups). Of the 51 reference ranges, the reference range for which TIR most correlated to SD for each group was referred to as "optimal reference range 2". Mean absolute deviation (MAD) correlated to SD ($r=0.995$, $P<0.001$; MAD = 0.87 × SD - 1.22) ($n=150$). "Margin" of "optimal reference range 1" (M1, mg/dl) tended to increase with increased target SD (mg/dl), from 42 for "target SD of 25" to 66 for "target SD of 50". Target SD correlated to M1 ($r=0.92$, $P<0.001$; M1 = 1.31×target SD + 5.56) ($n=26$). The optimal cutoff values of TIR for "optimal reference range 1" was 86.8±4.6 in 26 target SD. "Margin" of "optimal reference range 2" (M2) tended to increase with increased mean of SD, from 35 for "mean of SD of 30.6" to 64 for "mean of SD of 47.7". Mean of SD correlated to M2 ($r=0.96$, $P<0.001$) ($n=41$). SD means difference from M. If "optimal reference range 1" is used as an alarm threshold in a personal CGM and TIR for "optimal reference range 1" > 80–90% is achieved, SD below the target may be achieved. The mean of SD in study participants may affect the M2.

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EP495

Ultrasound of sternocleidomastoid muscle may predict and diagnose type 2 diabetes mellitus and prediabetes

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In order for type 2 diabetes to occur, insulin resistance occurs first, which often occurs from an increase in fat deposition in the liver and the pancreas, and with this resistance. It is universally agreed that diabetes diagnosis is by analyzing blood glucose. The ultrasound technology often helps in diagnosis and quick decision-making in the treatment of many diseases. It can tell us about the muscles' echogenicity.
Materials and Methods
400 patients followed in a private clinic in observational prospective study. Patients have been categorized into 4 groups. making neck ultrasound for all participants.
Results
The results exhibit a statistically notable difference between prediabetic patients and normal weight control as regards sternocleidomastoid muscle echogenicity with increased muscle echogenicity in prediabetic group and normal echogenicity in normal weight control group with P value less than 0.0001.The results exhibit a statistically notable difference between prediabetic patients and obese control as regards sternocleidomastoid muscle echogenicity with increased muscle echogenicity in prediabetic group and normal echogenicity in obese control group with P value less than 0.0001. The results exhibit a statistically notable difference between diabetic patients and normal weight control as regards sternocleidomastoid muscle echogenicity with increased muscle echogenicity in diabetic group and normal echogenicity in normal weight control group with p value less than 0.0001. The results exhibit a statistically notable difference between diabetic patients and obese control as regards sternocleidomastoid muscle echogenicity with increased muscle echogenicity in diabetic group and normal echogenicity in obese control group with P value less than 0.0001.
Conclusion
As we are in great need of new ways to diagnose and treat type 2 diabetes mellitus. Ultrasound of sternocleidomastoid muscle provides an effective way of predicting and diagnosing type 2 diabetes.

Keywords: type 2 diabetes mellitus, sternocleidomastoid, ultrasound
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EP496

H syndrome presenting as juvenile diabetes in algerian man

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Introduction
H syndrome is a non-Langerhansian histiocytosis secondary to a mutation in the SLC29A3 gene encoding the nucleotide transport protein hENT3, It is a rare disease with a prevalence of 1 case 1,000,000 mainly characterized by hyperpigmentation, hypertrichosis and hepatosplenomegaly with endocrine manifestations including hypogonadism, short stature and insulin dependent diabetes mellitus. We report the case of a 20-year-old male who was admitted to our endocrinology department for chronic glycemic imbalance. Clinical case: This is a 20 year old patient, with a history of Mutism with deafness diagnosed at the age of 2 years, known type 1 diabetic since the age of 10 years put on insulin therapy basal bolus scheme. In addition, the patient presents a picture of exocrine pancreatic insufficiency under creon since 5 years. We had evoked a wolfram diabetes, in front of the presence of the deafness and the diabetes type 1. During the clinical examination we noticed hyperpigmented patches on the thighs and legs, as well as hypertrichosis. This led to the consideration of syndrome H as a possible diagnosis. A skin biopsy was performed on the hyperpigmented patch, which came back positive for markers: PS100 and CD68, confirming the diagnosis. The genetic study could not be done.
Conclusion
Although considered a very rare disease, this syndrome is probably not diagnosed and therefore not reported. The characteristic skin manifestation as well as genetic testing are essential for diagnosis. The hearing loss also varies in severity and may go unrecognized.

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EP497

Meningoencephalitis revealing type 1 diabetes

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Introduction
Meningoencephalitis (ME) is defined as an inflammatory process of the brain and meninges, most often secondary to an infection, or more rarely to a dysimmune process. From a clinical point of view, ME is defined by the association of a neurological disorder (disorder of consciousness, convulsion) with a febrile meningeal syndrome.
Case Report
The patient was 24 years old and had no previous medical history. He was admitted to the emergency room with abdominal pain and vomiting, which had been present for 2 days prior to his admission in a febrile context. On examination, the patient was initially conscious, dehydrated, with meningeal stiffness, capillary blood glucose was 3.56 g/l, urine dipstick showed glycosuria with 3 criss-cross of acetone. The workup showed a hyperglycemia at 4.8 g/l, a normal ionogram, CRP at 320 and hyperleukocytosis at 130,000 predominantly PNN, a urinary tract infection at ECBU with leukocyturia at 22,000 and presence of BGN, the workup was completed by a cerebral CT scan which came back normal, and a lumbar puncture in favor of bacterial meningitis, the patient was put on rehydration, The patient was put on rehydration, insulin therapy, and C3G meningitis dose, the evolution was marked by the appearance of consciousness disorders, the patient was transferred in intensive care unit, intubated, sedated, and put on insulin therapy in SAP, the culture of the ECBU and lumbar puncture objective a sensitive Escherichia coli infection. It is therefore a meningoencephalitis complicating a urinary infection with E-coli and revealing a type 1 diabetes.
Discussion
Infectious etiology of meningoencephalitis was found in 42% of cases, a dysimmune etiology was identified in 21% of cases and in 37% of cases the etiology remained undetermined (1). The most frequent infectious causes were HSV-1, followed by VZV and Mycobacterium tuberculosis, while E-coli meningoencephalitis remained relatively rare. Cerebral CT scan is not very helpful for encephalitis and must be systematically performed before any lumbar puncture.
Conclusion
The search for meningeal stiffness in diabetic ketosis should be systematic, as should the search for a pulmonary, urinary or digestive infection. Neuro-meningeal infection can complicate a urinary infection; thus, the mortality rate of E- coli meningitis and meningoencephalitis remains very high.

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EP498

Stiff person syndrome revealing a LADA

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Introduction
Stiff-Person Syndrome (SPS) is a rare autoimmune neurological disorder that can be associated with other autoimmune diseases including type 1 diabetes mellitus (T1DM). The presence of alternative forms of autoimmune diabetes, such as latent autoimmune diabetes in adults (LADA) in SPS, is not well described.
Case Report
A 63 years old male patient, his medical and family histories were non-specific.He developed progressive rigidity in truncal and lower-limb musculature and episodic brief truncal associated to polyuro-polydipsic syndrome.MRI of the brain and spinal cord was without anomalies, the diagnosis of stiff person syndrome was suspected, an anti GAD assay was requested returning >3000 units/ml.As part of exploration of polyuro polydipsic syndrome, a glycated hemoglobin was done returning to 8%.
Discussion
Stiff-person syndrome (SPS) is a rare neurological disorder, which is an autoimmune disorder frequently associated with the presence of serum anti-glutamic acid decarboxylase (GAD) antibody. Solimena et al was the first to describe the important link between insulin-dependent diabetes mellitus, and SPS in 1988. GAD is an endogenous enzyme that catalyzes the production of γ-aminobutyric acid (GABA), a major neurotransmitter of the central nervous system, and it is also found in pancreatic beta cells.it is a common autoantigen in SPS and type1 diabetes mellitus. They are detected in 80% of patients with newly diagnosed T1DM; but the titer of anti-GAD is much higher (around 50-100 fold) in SPS than in Type1 diabetes mellitus. The presence of the autoimmune anti-GAD may lead to disruption of neuron ,beta cell function and destructs insulin secretion.
Conclusion
Despite the fact that LADA and Stiff Person Syndrome are both autoimmune diseases characterized by the presence of anti-GAD, the rates of co-occurrence of SPS and LADA remain unknown.
Reference
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EP499

Case report: Inaugural ketosis revealing diabetes secondary to Klinefelter's syndrome

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Introduction
Klinefelter's syndrome is the most common male chromosomal abnormality. Several metabolic manifestations are observed during this syndrome including diabetes mellitus. We report the case of a patient who presented with inaugural ketosis revealing diabetes secondary to Klinefelter syndrome.
Observation
38-year-old patient followed for primary infertility for 6 years, alcoholics and smokers who have been weaned for 3 years, two sisters with a T2DM profile. He presented for 3 weeks a polyuro polydipsia syndrome without weight loss, vomiting or abdominal pain, referred after testicular biopsy for hyperglycemia at 4 g/l, glycosuria and acetonuria at 2× and bicarbonates at 25. The clinical examination noted a Klinefelter's profile, protruding superciliary arches, BMI at 31 kg/m^2, a pathological waist circumference at 102 cm, bilateral gynecomastia, micropenis and a Tanner stage at G2P4. On work-up: CRP: 6 mg/l; TSH = 1.93 µg/ml, cortisol: 120 µg/l; FSH: 36.8 UI/l; LH: 14.9UI/l; Testosterone: 0.08 µg/l; prolactin: 5.19 ng/ml; calcemia: 92 mg/l, Creatinine = 5 mg/l (GFR: 170 ml/mn), CT: 1.96 g/l; TG: 2.92 g/l; HDL: 0.34 g/l; LDL: 1 g/l. HbA1c = 14.8%. Testicular ultrasound showed small testicles. Spermogram: total azoospermia; Karyotype: homogeneous klinefelter 47, XXY. The treatment consisted in the correction of ketosis and then put on Mixtard30 (30-0-18), and Metformin 1000mg in progressive dose. The evolution was favorable with normalization of the glycemic values.
Discussion and Conclusion
In Klinefelter's syndrome, type 2 diabetes and carbohydrate intolerance are observed, with frequent hyperinsulinism and a peripheral insulin resistance mechanism, the clinical expression of which is a metabolic syndrome. Klinefelter's syndrome, although rare, is the most frequent male chromosomal abnormality, which is diagnosed late and often at the time of primary infertility. It may be associated with metabolic disorders and particularly diabetes due to insulin resistance observed in Klinefelter.

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EP500

Glucocorticoid-induced diabetes

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Introduction
The aim of this study was to investigate the characteristics of glucocorticoid-induced diabetes (GCID) in 18 non-diabetic patients before the initiation of corticosteroid therapy.
Patients and Methods
It is a retrospective study including non-diabetic hospitalized patients who developed diabetes after initiation of corticosteroid therapy.
Results
Eighteen patients (5 males/13 females) with a mean age of 59.5 years were included. A family history of diabetes was noted in 7 cases. Associated

cardiovascular risk factors were hypertension in 4 patients (18%), dyslipidaemia in 3 patients (16%), obesity in 7 patients (38%). Corticosteroid therapy was initiated with methylprednisolone boli in 18% of cases. In 72% of cases, patients received oral prednisone at a dose of 1 mg/kg/day. The median time to onset of GCID was 130 days (range 3-510 days). Thirteen patients (72%) developed an early GCID (within the first 3 months). The mean dose of prednisone at the time of the diagnosis was 0.7 mg/kg/day. Of these 18 patients, 7 received insulin therapy, and 6 received oral antidiabetic drugs. Five patients were managed by a diet only. The mean glycated haemoglobin was 7.3%.
Conclusion
GCID is a common complication occurring often after the age of 55 years and within 3 months of starting corticosteroid therapy. A later onset is also possible. A high initial dose of corticosteroids increases the risk of early GCID.

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EP501

Glycemic variability in a group of Tunisian adolescents with type 1 diabetes mellitus

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Introduction
Glycemic variability (GV), defined as an integral component of glucose homeostasis, is emerging as an important metric to consider when assessing glycemic control in clinical practice. The aims of our study were to study glycemic variability among a group of adolescents with type 1 diabetes and to determine the factors influencing this parameter.
Method
This is a cross-sectional analytical study, conducted at the National Institute of Nutrition in Tunis during the year 2021, including type 1 diabetic patients who underwent continuous glucose monitoring for 6 days. We analyzed the continuous glucose monitoring CGM data for each patient and we calculated the coefficient of variability by dividing the S.D. by the mean glucose and multiplying by 100 to get a percentage.
Results
Our study included 81 patients with type 1 diabetes, of which 47 are girls and 34 are boys. The average age was 16.6 ± 2 years and the mean duration of diabetes was 6.26 ± 4 years. The age of onset of diabetes varies between 1 and 18 years with an average of 10.4 ± 4 years. Patients with glycated hemoglobin (HB1AC) greater than 7% had an average coefficient of glucose variability (CV) of $39 \pm 12\%$ while those with a HB1AC less than 7% had an average CV of $40 \pm 11\%$. The majority of patients had glycated hemoglobin greater than 7% (89% of patients). Furthermore; More than half of the patients had a coefficient of variation of glucose (CV) greater than 36%. The average CV was $39 \pm 12\%$. The CV was significantly correlated to the age of patients ($r=0.25$ $P=0.025$) and to the duration of diabetes ($r=0.35$ $P=0.001$). However, CV was negatively correlated with age of diabetes onset ($r=-0.23$ $P=0.036$). The glycated hemoglobin was correlated to the CV ($r=0.22$ $P=0.049$).
Conclusion
HbA1c was traditionally considered as the gold standard for assessing glycemic control. GV is a more meaningful measure of glycemic control than HbA1c in clinical practice, and is without doubt now being recognized.

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EP502

Assessment of laboratory characteristics of patients with severe COVID-19 infection: focus on in-hospital hyperglycemia

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Both hyperglycemia and in-hospital hypoglycemia are associated with poor hospital outcomes and increased healthcare costs. The effect of hypoglycemia may be due to the severity of the infectious disease and the high incidence of comorbidity. **The aim** of the study was to study the possible relationship between the severity, duration and compensation of hyperglycemia with the course of Covid-19.
Materials and methods
A retrospective analysis of data from primary medical records of 320 patients with Covid-19 infection, who, taking into account their severity of condition, received medical care in the intensive care unit of the infectious hospital in Minsk from June 2020 to March 2022, was carried out. There were 3 groups: 224 people with hospital hyperglycemia – the main group; 51 patients with a history of DM and/or newly diagnosed DM (comparison group); 45 people without glycemic disorders (control group).
Results and discussion
In patients with HH, a more frequent used of tocilizumab and remdisivir, what may indicate a higher severity of the disease course Patients in HH and DM groups showed similar results according to the studied criteria, which confirms the significance of the selected glucose level (more than 7.8 mmol/l) as a threshold for verifying glycemic disorders. In 15.6% of patients with normoglycemia, glycemic levels were less than 4.0 mmol/l. In the present study, lethality in the HH group was the highest and exceeded the control group by 3.5 times, and the indicator of the group with DM by 1.3 times ($P<0.001$). Comparing glycemia levels was found that in the DM group the glucose value was the highest (7.7 (6.1; 12.9) mmol/l vs. 7.0 (5.9; 8.4) mmol/l in the in HH group). Patients with HH and DM had higher levels of procalcitonin, CRP, LDH, neutrophils, more pronounced lymphopenia, which indicated a more pronounced inflammatory process. The level of D-dimers was also higher in the groups of patients with DM and HH.
Conclusions
According to the study, 70% of patients with severe COVID-19 had newly diagnosed hyperglycemia, 15.6% of patients in the control group had glycemia less than 4.0 mmol/l. The data obtained indicate the need for screening of glycemia and its multiple studies during the day in hospitalized patients with severe COVID-19.

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EP503

Eating disorders in patients with type 1 Diabetes

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Introduction
Eating disorders (ED) are common in type 1 diabetes (T1D). The aim of our study was to determine the frequency of eating disorders in a T1D population.
Methods
This was a descriptive prospective study conducted in Department C of the National Institute of Nutrition in Tunis, including 52 patients with T1D. We evaluated the prevalence of eating disorders using the 'Eating Disorder screening DEPS-R Scale'. A score $>$ 20 indicates an ED. Clinico-metabolic characteristics were collected from medical records. Glycemic imbalance was defined by an HbA1C$>$7%.
Results
The average age was 28 ± 12 years. The sex ratio was 0.57. The body mass index (BMI) was between 16.72 and 29.6 kg/m^2. 10.1% of patients were overweight. The average duration of diabetes was 10 ± 6 years. 48% of patients were treated with insulin analogues. Micro and macro vascular degenerative complications were frequent at 40.3% and 7.6% respectively. Diabetes was unbalanced in 76.9% of cases with an average HbA1C of 10.3%. ED were frequent by 80.7%. In patients with an ED, diabetes was unbalanced in 72% of cases. We did not show a significant association between BMI and ED. However, glycemic imbalance and ED were significantly associated ($P<10^{-3}$).
Conclusion
ED could disrupt glycemic control in patients with T1D. Thus, their systematic screening is essential.

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EP504

Hyperglycemia in patients with severe COVID-19

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Objective
Stress hyperglycemia and decreased control of diabetes mellitus are recorded in severely hospitalized patients and are associated with an increased complications level, length of hospitalization and mortality. Clinical evidence suggests an increased prevalence of hospital hyperglycemia in patients with COVID-19 and a difference from typical stress hyperglycemia.
Materials and methods
We studied 219 moderate and severe hospitalized COVID-19 patients at Minsk City Maternity Hospital N2 in October-November 2021. A retrospective analysis from medical documents was performed.
Examination
Albumin, total calcium, creatinine, alkaline phosphatase, total protein, urea, creatinine, procalcitonin, CRP, total bilirubin, glucose, ALT, AST, ferritin, cretincrinase, uric acid, PCR-test, KT.
Results
All patients were PCR positive, average age 61.1 ± 10.19 years. Patients were hospitalized with moderate or severe COVID-19 pneumonia on days 2–16 of illness. BMI = 28.4 (26.3–32.0) kg/m2, glucose = 6.1 (5.4–7.3) mmol/l. Type 2 diabetes mellitus was registered in 31 (14.2%) patients; type 1 diabetes mellitus was registered in 3 (1.4%) patients. Hyperglycemia was registered in 163 patients (74.4%), including patients with type 2 diabetes mellitus and type 1 diabetes mellitus. 21 patients with newly reported hyperglycemia (15.9%) had glucose > 11.1 mmol/l and basis-bolus insulin therapy was prescribed. Analysis of the medical data of these patients and HbA1c < 5.7% indicate that these patients did not have diabetes mellitus before COVID-19. At the end of COVID-19 treatment, 14 (66.7%) patients did not require glucose-lowering treatment.
Conclusion
The results of the study indicate a high prevalence of newly diagnosed hyperglycemia in moderate and severe COVID-19. The identified hyperglycemia in COVID-19 differs from typical stress hyperglycemia and from the manifestation of type 2 diabetes mellitus and type 1 diabetes mellitus and needs further analysis.

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Prevalence of hypokalemia in patients with diabetic ketoacidosis

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Background/aims
Although patients with diabetic ketoacidosis (DKA) are expected to have total body potassium depletion, measured levels may be normal or elevated due to extracellular shifts of potassiumsecondary to acidosis. We aimed to examine the prevalence of hypokalemia in patients with DKA at presentation and during the treatment.
Methods
This is a retrospective cross-sectional descriptive study concerning all patients hospitalized in the Endocrinology Department for DKA between October 2021 and January 2022. Initial kalemia levels (k+) on presentation and those after treatment were determinated on AU 680® Beckman Coulter. Hypokalemia was defined using the criteria set forth by the American Diabetes Association (ADA) as measured serum potassium less than 3.3 mmol/l. The data were analyzed using SPSS26.
Results
A total of 30 patients were hospitalized for DKA. The mean age of the group was 26.73 ± 10.41 years. The mean potassium level was 3.73 mmol/l (range 2.3 to 5.3; s.d. ± 0.72). Among patients, 26.66%had hypokalaemia (k+ < 3.3 mmol/l), 16.66% had k+ between 3.3 and 3.5 mmol/l. In 26.66% of cases the k+ was between 3.5 and 4 mmol/l and 16.66% of patients had k+ between 4 and 4.5 mmol/l. In 10% of patients the k+ was between 4.5 and 5 mmol/l. Only one patient was presented with hyperkalemia. The mean age of the group who presented hypokalemia was 27 125 years ± 8.62 and 50% of them were Type 1 diabetes. None of the patients had neuromuscular or electrical signs of dyskalemia. During treatment, the mean k+ was 3.43 mmol/l (range 2.5 to 4.1; s.d. ± 0.4). The prevalence of hypokalemia was 33.33%. Among the patients who had hypokaliemia at presentation, 75% of them developed an hypokaliemia during treatment. And among the patients who had normal values of k+, 18.18% of them developed an hypokaliemia during treatment. The mean of duration of insulin therapy were 38.5 (± 24.21) hours and 30.69 (±18.77) hours ($P = 0.039$) respectively for the group who presented hypokalemia and for the group with normal k+ during the treatment. Also the group who presented hypokalemia during the treatment received higher total insulin dose infusion (85.09 ± 47.30 units vs 52.66 units ± 29.80);($P = 0.039$).
Conclusion
Hypokalemia was observed in 26.66% of patients with DKA. Further research is needed to better determine the risks and benefits of administering insulin before obtaining serum potassium values. The strategy of lowering insulin infusion rate in patients with significant hypokalemia during DKA treatment should require further evaluation.

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EP506

Celiac disease in adult patients with type 1 diabetes: screening and clinical and paraclinical profile

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Aims
Screening for celiac disease in adult type 1 diabetics and studying its clinical and paraclinical profile.
Patients and methods
Cross-sectional descriptive study conducted among 150 adult type 1 diabetic patients followed in Department A of the National Institute of Nutrition of Tunis. All patients underwent serological screening for celiac disease.
Results
The prevalence of histologically confirmed celiac disease was 3.33% while 4% had positive celiac disease serology. The average age of patients with celiac disease was 34.8 years with an average BMI of 22.71 ± 2.76 kg/m^2 and four out of five patients had a normal BMI and diabetes evolving for more than 5 years. Three out of five patients had uncontrolled diabetes and two had recurrent hypoglycaemia. Among the five diabetics with confirmed celiac disease, only one patient showed classic signs of celiac disease. Of the others, one patient was asymptomatic and three showed non-classical signs of celiac disease.
Discussion
The recommendations of the various learned societies on the methods of screening for celiac disease in adult patients with type 1 diabetes are still controversial, hence the need for more studies on this subject [1-7].

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EP507

Diabetes and fasting during the SARS-COV 2 pandemic

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Introduction
The covid-19 pandemic has affected the diabetic population and their glycemic control, in particular Muslim diabetics fasting during the month of Ramadan. Our objective was to assess the glycemic control between Ramadan 2020 (April) and Ramadan 2021 (April) and to determine the impact of the pandemic on the Fasting authorization.
Methods
This is a prospective study including 30 diabetic patients followed at department A, at the National Institute of Nutrition in Tunis. Each patient underwent a clinical examination and a blood test.
Results
The mean age was 59.53 + 11.16 years. The mean diabetes duration was 9.7 ± 6.9 years. The majority of patients were type 2 diabetics (93%). More than a quarter were on insulin (27%) ($n = 8$). Only three patients (10%) had a SARS-cov2 infection. Before Ramadan 2020, the mean fasting Glycemia was 9.47 + 2.8 mmol/l and the mean HbA1c was 8.25 + 1.52%. Among our patients, 43% ($n = 13$) had HBA1c in the objectives. Ramadan 2020 fasting was authorized in 43% of patients (those with HBA1c in target) and antidiabetic treatment was appropriate in 90% of cases. The 2020 Ramadan fasting was complicated by hypoglycemia and hyperglycemia in 7% and 13% of cases respectively. only one patient stopped the fasting. Before Ramadan 2021, the mean fasting Glycemia was 10.51 + 3.2 mmol/l and the mean HBA1C was 8.15 + 1.6%. Before Ramadan 2021, glycemic target was reached in 48% of patients ($n = 14$), with an improvement of 5%.
Conclusion
The period of the pandemic has influenced the glycemic control in our diabetic population who practice Ramadan fasting. More studies will be needed to further assess this interference.

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EP508

Type 2 diabetics on high doses of insulin: what therapeutic solution?

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Introduction
Glycemic control in type 2 diabetics on insulin is a real therapeutic challenge. The aim of this study was to determine the clinical profile of type 2 diabetic patients on high doses of insulin and to assess their glycemic control after a reduction in insulin doses.
Method
It was a prospective study conducted in the Diabetology Department of the National Institute of Nutrition in Tunis with type 2 diabetic patients (T2DM) hospitalized on a high dose of insulin (≧ 0.5 IU/kg/d). Insulin dose reduction and dietary education were performed in all patients included in the study. Insulin doses were subsequently adjusted according to pre- and postprandial capillary blood glucose levels.
Results
We included 48 patients with a mean age of 59 ± 11 years [22;78] and a sex ratio (M/F) of 0.37. The mean age of diabetes was 19 ± 8 years. The mean time of permanent insulin therapy initiation was 12 ± 8 years. Metformin was prescribed in 56% of T2DM patients. Poor adherence to dietary rules was found in the majority of T2DM patients (91%), most of whom were sedentary (82%). Obesity was present in 67% of diabetics: it was abdominal in 75% of cases. Hypertension, dyslipidaemia and hypothyroidism affected 67%, 81% and 19% of diabetics, respectively. The mean glycated haemoglobin level was 10.4 ± 1.9%. The mean insulin dose at admission was 1.14 ± 0.26 IU/kg [0.8;2.21]. A mean rate of insulin dose reduction was 30.6 ± 14.2%. At the end of the hospitalization period: a statistically significant decrease in preprandial ($P = 0.007$) and postprandial ($P = 0.002$) blood glucose levels was noted.
Conclusion
Insulin overdose is common in insulin-requiring type 2 diabetics without any real benefit for glycemic control, but with a risk of aggravating the often present overweight.

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EP509

Metabolic profile of T2D patients on liraglutide: About 31 cases

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Introduction
Liraglutide has shown several benefits in diabetic patients, both in terms of glycemic profile and metabolic control. The objective of our work is to show the effects of liraglutide on the metabolic profile of obese T2D patients.
Materials and methods
This is a prospective study involving 31 obese T2D patients followed at the Department of Endocrinology and Metabolic Diseases CHU IBN ROCHD from January 2018 to December 2022. The data analysis was done with the Excel software in its 2021 version.
Results
The mean age was 49.44 years, Sex Ratio: M/F of: 1/4, the duration of diabetes was on average 12.17 years, the mean duration of treatment with liraglutide was 3 years. All our patients were obese with an average BMI of 39 kg/m2 and a waist circumference of 121 cm. All of our patients were unbalanced with an average Hb1c of 10%. The metabolic balance objectified dyslipidemia in 24 patients or 82.7% with a mean cholesterol level of 1.9 g / l, mean triglyceride of 1.47 g / l, mean HDL of 0.49 g / l and mean LDL level of 1.11 g / l. Arterial hypertension was objectified in 13 patients or 44.8% all monotherapy, hyperuricemia was objectified in 4 patients or 13.8% with an average uric acid level of 58.91 mg / l. The majority of patients or 75.8% were on insulins either in basal bolus or bed time regimen in combination with metformin and sulfonamide and 24.2% are on dual therapy metformin sulfonamide. After the introduction of liraglutide treatment, there was a decrease in BMI to 37.74 (−1.26), a decrease in waist circumference to 111.25 (−5.39), a decrease in Hba1c to 7.47 (− 2.53%), a decrease in uric acid to 55.33 (−3.58), an improvement in lipid profile with a decrease in LDL to 0.89 g / l (−0.22), a decrease in CT to 1.72 g / l (−0.18), a decrease in TG to 1.4 (−0.05) and an improvement in HDL to 0.52 (+0.03). Regarding the treatment of diabetes, 23.33% of our patients had benefited from insulin withdrawal.
Conclusion
Treatment with GLP-1 analogues offers a new therapeutic option of major interest in the management of type 2 diabetes.

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EP510

New indication for long-acting second-generation basalinsulin analog?

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Introduction
Although skin reactions relating to insulin injection have decreased since the prescription of human insulin and the use of highly purified insulin, they are still described in the literature. They can lead to significant problems with glycemic control. The challenge is to recognize the type of reaction that is occurring and identify the type of insulin formulation that avoids these reactions.
Case-report
A 64-year-old patient, with type 2 diabetes for 24 years on premixed human insulin for 10 years, presented with pruritic erythematous lesions at insulin injection sites that appear few hours after the injection and persist for a few days. They improved under topical corticosteroids. IgG-mediated delayed hypersensitivity (type III hypersensitivity) was suspected. The reaction was induced bythe different formulations of insulin and we could not recognize whether the insulin or an excipient was incriminated. We eliminated an allergy to protamine, metacresol and zinc as well as a dermographism. This left us questioning the diagnosis of allergic reaction and we resorted to a skin biopsy. It showed a cutaneous panniculitis which is an inflammation of the subcutaneous fat that results from local trauma caused by both physical and chemical insults. Initially, the management wasto split the total daily dose of Insulin glargine 100 units/ml LANTUS®in two different sites at the same time. There action was less severe. Then, the use of Insulin glargine 300 units/ml TOUJEO® allowed to avoid this reaction.
Discussion and conclusion
The most frequent skin reactions relating to insulin injection are allergic. However, it is important for healthcare professionals to be mindful of cutaneous panniculitis as apossible complication of insulin injections. Very few similar case reports were published. It remains possible that it is under-recognized. The absence of reaction under the long-acting second-generation basal insulin analog

TOUJEO® (Insulin glargine 300 units/ml)may be explained by the fact that this type of Insulin formulation allows continuous release of insulin from the adipose tissue. This allows to avoid the local trauma caused by the peaks of Insulin-release.

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EP511

Autoimmune polyendocrinopathy syndrome type 4

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Introduction
Autoimmune polyendocrinopathy syndrome (APS) type 4 is rare, characterized by an association between an autoimmune endocrine disease with another endocrine or non-endocrine autoimmune disease, and this association cannot be attributed to APS type 2 or 3. We report the observations of 3 cases with APS type 4.
Cases presentations
Case N 1:
Patient 16 years old, type 1 diabetic for 9 years under insulin therapy, with alopecia areata for 4 years under Methotrexate 25 mg/week and folic acid 5 mg/week
Clinical examination showed alopecia of the scalp, the eyelashes and the eyebrows. Screening for other polyendocrinopathies was normal.
Case N 2:
24-year-old female patient, type 1 diabetic for 16 years on insulin therapy, treated for celiac disease on a gluten free regime for 14 years.
Case N 3:
Patient aged 54, followed for primary biliary cholangitis (PBC) at the stage of cirrhosis, who reported signs of hypothyroidism, on clinical examination: bradycardia at 55 bpm, palpable thyroid. The workup revealed autoimmune Hashimoto's thyroiditis.
Discussion
Autoimmune polyendocrinopathies (APS) represent a heterogeneous group of diseases characterized by two or more endocrine deficits related to an autoimmune mechanism, often associated with other non-endocrine autoimmune diseases. The classification by Neufeld and Blizzard identifies four types: APS type 1 is defined by the presence of at least two manifestations of a triad: adrenal insufficiency, hypoparathyroidism and mucocutaneous candidiasis. APS type 2 is the most common, and combines adrenal insufficiency with either type 1 diabetes or dysthyroidism, or both. APS type 3 is the combination of a dysimmune endocrinopathy (other than adrenal insufficiency) and dysthyroidism, and APS type 4 includes any other combination of autoimmune diseases. Our first two patients had T1DM associated with another non-endocrine autoimmune disease, and our third patient had Hashimoto's thyroiditis associated with PBC, this combination leads us to a diagnosis of APS type 4.
Conclusion
In any patient with autoimmune disease, a regular follow-up is indicated to identify the emergence of new autoimmune diseases.

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EP512

Evaluation of Socio-demographic, clinical and biochemical characteristics of patients with Non Alcoholic Fatty Liver Disease and Diabetes who are attending the diabetic clinic in a tertiary care institute in Colombo, Sri Lanka

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Background and objectives
Non-alcoholic fatty liver disease (NAFLD) is highly prevalent in patients with diabetes as well as the vice versa. It is crucial to identify the characteristics of this group of patients in order to prevent the development, the progression as well as the complications of the disease. We have studied characteristics of patients having both NAFLD and diabetes who are attending a tertiary care institute in Sri Lanka.
Methods
A descriptive cross sectional study was conducted from August 2020 to March 2021 at the Diabetes Unit of the National Hospital of Sri Lanka. All the patients who met the inclusion and exclusion criteria who met the diagnosis of NAFLD according to the NHANES III criteria or/and the USS criteria were recruited in to the study. After obtaining informed written consent, the data was collected using an interviewer administered questionnaire. Categorical and numerical variables were analyzed using Chi-square and independent sample t-tests respectively.
Results
Seventy fur patients who met the diagnostic criteria of NAFLD were enrolled in to the study. The mean age was 56.8 years (range 23–79) and 77% were females. The mean weight was 66.6 (s.d. = 12.1)kg and BMI was 27.4 (s.d. = 4.7)kg/m^{-2}. 47.3% met both biochemical and USS criteria. Furthermore, 12.2% ($n = 9$) met only the biochemical criteria while 40.5% ($n = 30$) met only the USS criteria. Majority (67.6%) were receiving a monthly income of SLR $< 30\,000.00$ per month and majority were unemployed (73%). A larger proportion were having type 2 diabetes for > 10 years. Mean HbA1c was 8.9 (s.d. = 1.9)%.
Conclusions
NAFLD with diabetes is associated with overweight, poor glycaemic control, poor income and unemployment indicating the future focus groups for disease prevention and management. Further large scale studies are needed to evaluate the risk factors in more detail.

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EP513

Can prebiotics improve weight loss in obese patients?

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Background
Prebiotics are compounds in food that induce the growth of beneficial microorganisms such as bacteria and fungi, which are essential for the proper functioning of the microbiota. The objective of our work was to evaluate the effect of prebiotics intake on anthropometric parameters in addition to a weight loss program.
Methods
This is an interventional study involving 30 obese patients consulting the obesity unit of the Institute of Nutrition of Tunis during the period from May to August 2022. Patients were divided into 2 groups matched for age, sex and BMI: diet alone and prebiotics (30 g of carob/d). Anthropometric measures (weight, waist circumference, BMI), body composition, and muscle strength (using handgrip dynamometer) were assessed at T0 and at one month after the intervention (T1).
Results
The mean age was 40.3 ± 6.7 years with a female predominance (80% of women). For the diet alone group, there was a significant decrease in body weight (-2.5 kg, $P = 0.001$), BMI (-0.9 kg/m^2, $P = 0.001$) and waist circumference (-1.7 cm, $P = 0.01$) between T0 and T1. For the prebiotic group, in addition to the significant decrease in weight (-2.2 kg, $P = 0.003$), BMI (-0.9 kg/m^2, $P = 0.001$) and waist circumference (-4 cm, $P = 0.03$), we have noticed a significant decrease in fat mass (-2.9 kg, $P = 0.001$) and percentage fat mass (-1.8%, $P = 0.001$), as well as a significant improvement in muscle strength ($+1.4$ kg, $P = 0.008$). Although the decrease in body fat and body fat percentage and the increase in muscle strength were significant in the prebiotic group and not in the diet alone group, the difference between the two groups was not significant.
Conclusion
For anthropometric parameters, the prebiotic group was not superior to the diet alone group.

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EP514

Can prebiotics improve daytime sleepiness in obese patients?

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Background
Excessive daytime sleepiness is a common complaint in obese patients affecting life quality. The objective of our work was to evaluate the impact of prebiotics intake on daytime sleepiness in addition to a weight loss program.

Methods
This is an interventional study involving 30 obese patients consulting the obesity unit of the Institute of Nutrition of Tunis during the period from May to August 2022. Patients were divided into 2 groups matched for age, sex and BMI: diet alone and prebiotics (30 g of carob/d). No patients took antibiotics during the intervention period and no patient stopped taking carob. Daytime sleepiness was assessed at T0 and at one month after the intervention (T1) using the Epworth sleepiness scale. A score ≥ 10 indicates excessive daytime sleepiness (EDS). The statistical level of significance was defined as $P<0.05$.
Results
The mean age was 40.3 ± 6.7 years with a female predominance (80% of women). EDS was found in 46.7% patients in each group at T0. There was a significant weight loss in each group (diet only group: -2.5 kg $P=\mathbf{0.001}$ and prebiotic group: -2.2 kg, $P=\mathbf{0.003}$). However, there was no statistically significant difference in weight loss between the two groups ($P=0.7$). For the diet alone group there was an improvement in the Epworth score between T0 and T1 that was not statistically significant (9.8 vs 8. 6, $P=0.06$). For the prebiotic group, we have noticed a statistically significant decrease in Epworth score (8.7 vs 7, $P=\mathbf{0.02}$) however, when comparing both groups, the difference was not significant ($P=0.06$).
Conclusion
It seems that prebiotics improve excessive daytime sleepiness in obese patients. Further studies are needed to understand the underlying mechanisms.

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EP515

Endocrine-disrupting chemicals and transgenerational inheritance of obesity

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Introduction
Epigenetics is defined as heritable changes in gene expression without changes in the DNA sequence. The transgenerational epigenetic inheritance of diseases is an emerging area of research. Multiple environmental factors including toxicants are associated with the transgenerational inheritance of increased disease susceptibility. Endocrine-disrupting chemicals (EDCs) are a heterogeneous group of exogenous chemicals or chemical mixtures that interfere with the action of hormones. The obesity pandemic cannot be explained solely by alterations in food intake and/or decrease in exercise. The present review explores the literature on transgenerational inheritance of obesity caused by EDCs.
Methods
A systematic search of literature was conducted using the search terms epigenetics, EDCs, obesogens, pregnancy, embryonic/fetal development, transgenerational inheritance, and obesity.
Results
By inducing epigenetic changes in germ cells (egg or sperm), the environment directly influences genetic variation, inheritance, phenotypic variation, and adaptation. The changes propagate through multiple generations without any new exposure to the initiating factor. The obesity pandemic coincides with the exponential increase in the number of EDCs present in the air, water, and food. Some EDCs called obesogens can promote weight gain despite normal diet and exercise. At least 50 obesogens have been identified. Exposure to obesogens (e.g., bisphenol A, tributyltin, and phthalates) during critical windows of embryonic/fetal development (e.g., Weeks 4–8) can induce transgenerational inheritance of increased obesity risk. Even if the exposure is removed, the transgenerational phenotype can persist through multiple generations. The proposed mechanisms implicated in transgenerational inheritance caused by EDCs include DNA methylation (the most studied mechanism), histone methylation, histone retention, chromatin structure alteration, and non-coding RNAs expression. With a direct exposure of the parents (considered the F0 generation) and the fetus (considered the F1 generation), the true transgenerational transmission is the F3 generation and beyond for the exposure of a pregnant female and the F2 generation and beyond for the exposure of a non-pregnant female or a male. Most reported human studies on transgenerational epigenetic inheritance are up to the F2 generation.
Conclusion
Exposure to a subset of EDCs called obesogens causes the metabolic programming of obesity and its transgenerational inheritance. Bisphenol A is one of the most widespread obesogens affecting humans. A better understanding of the mechanisms of the transgenerational inheritance is critical for the implementation of preventive strategies in the fight against obesity. Every effort should be made to minimize or avoid the exposure to obesogens, especially during the windows of sensitivity of the embryo/fetus.

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EP516

Impact of morbid obesity on kidney function in type 2 diabetic patients (Experience of the obesity unit CHU Mohammed VI; Marrakech) (About 31 cases)

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Introduction
Excess weight has become a major public health problem. Type 2 diabetes and obesity are known risk factors for kidney disease. The aim of this study is to determine the effect of obesity on glomerular filtration rate (GFR) and microalbiminuria in patients with diabetes.
Methods
This is a descriptive cross-sectional study conducted over three years in obese and type 2 diabetic patients hospitalized in the Endocrinology and Diabetology Department of the Mohamed VI University Hospital in Marrakech.
Parameters studied
* BMI, BP, Waist circumference, lipid balance. * Renal function. * GFR was determined by measuring plasma creatinine clearance (MDRD). * Microalbiminuria was measured on a 24-hour urine sample.
Results
-Population: 31 obese
-Sex ratio: 0.32
-Predominance: female
-Average age: 55.5 years (42–69 years).
- prevalence: severe obesity: 13.6% of diabetics morbid obesity: 86.36% of diabetics
-Average BMI: severe obesity: 38.1 kg/m2 morbid obesity: 52.5 kg/m2
-Average duration of diabetes: 8.4 years.
-The average GFR: 76.70 ± 20.41 ml/min for BMI $>$ 30 64.49 ± 13.26 ml/min for BMI $>$ 40
-. Prevalence of microalbiminuria:
* in type 2 diabetics with severe obesity: $21.13 \pm 6.85\%$
* in type 2 diabetics with morbid obesity: $55 \pm 11.45\%$.
Discussion
Obesity contributes to the parallel increase in the prevalence of chronic kidney disease, through: nephropathy associated with type 2 diabetes and hypertension. The existence of a metabolic syndrome, as well as the constant inflammatory state in obese type 2 diabetics, contributes to the development of glomerular sclerosis lesions. In our series we observed an interaction between the effect of obesity and type 2 diabetes on GFR. We also observed a strong interaction between the effect of obesity and T2DM on renal function with a reduction in GFR and an increase in microalbiminuria in morbidly obese patients.
Conclusion
Obesity is not only a cardiovascular risk factor, but also a renal risk factor. It is therefore essential to detect and treat high-risk patients. Therefore, testing for proteinuria and measuring renal function is indicated in all obese patients.

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EP517

Obesity and metabolic syndrome in patients with non-functioning pituitary adenomas

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Objective
To assess the prevalence of obesity and metabolic disorders in patients with non-functional pituitary adenomas (NFPA)
Patients and methods
A retrospective descriptive study of 35 patients followed for NFPA between 2000 and 2022. Metabolic syndrome was established according to the National Cholesterol Education Program Adult Treatment Panel III criteria.
Results
The mean age was 52.1 ± 11.4 years, with a male predominance (61.3%). Ninety percent were macroadenomas. The mean weight was 76.8 ± 15 kg corresponding to a mean BMI of 28.3 ± 5 kg/m^2. Obesity (40%) or overweight (26.7%) was frequently reported. The majority of obese patients were classified as grade 1 (66.7%). The mean waist circumference was 99.8 ± 13.4 cm with an android distribution of fat in 54.5% of

the patients with NFPAs. The frequency of hypertension was 16.1%. Glucose metabolism disorders were diagnosed in 34.5% of patients with a mean fasting blood glucose level of 5.7±2.4 mmol/l. Lipid metabolism was disturbed in 53.8% of cases. HypoHDLaemia and hypertriglyceridemia were observed in 36.4% and 11.5% of cases, respectively. Mixed hyperlipidemia affected 15.4% of patients. The overall prevalence of metabolic syndrome in our series is estimated at 16.7%.

Discussion

The mass effect of NFPAs is thought to be the cause of numerous hypothalamic dysregulations altering the biological circadian rhythm (waking-sleep, hunger-satiety, energy balance, etc...). These hypothalamic disturbances aggravate the metabolic risk in this population, who is particularly exposed to obesity and dyslipidemia. This situation would be further exacerbated by physiologically imperfect (glucocorticoids) or neglected (GH substitution) hormone substitutions.

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EP518

The effectiveness of a comprehensive rehabilitation program on the balance function in patients with obesity

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Objectives

The study of the influence of a new complex method of physical therapy with the inclusion of balance therapy with biofeedback and kinesihydrotherapy on the human balance function.

Material and methods

The study included men and women aged 40 to 65 years with a body mass index $\geq$30 kg/m^2. Research methods included anthropometry, stabilometry. The patients were further divided into two groups by simple randomization. Patients of both groups underwent a two-week course of medical rehabilitation. Patients of the main group received 4 methods of physical therapy: balance therapy, group classes in kinesihydrotherapy, group classes in a special complex of therapeutic exercises in the hall, aerobic exercises on a stationary bike or treadmill. The patients of the comparison group were treated only with the use of aerobic exercises and therapeutic exercises in the hall according to the same methodology and with the same number of procedures as in the main group. Dynamic observation was carried out at the beginning and after 14 days.

Results

According to the data, we obtained an improvement in the balance function on the 14th day of the study in terms of spread along the front ($P=0.028$) and the spread along the sagittal ($P=0.043$). Significantly improved indicators in the main group in terms of the average speed of movement of the center of pressure ($P=0.018$) and the speed of movement of the statokinesiogram ($P=0.028$), indicators of the area of the ellipse ($P=0.018$).

Conclusions

The new comprehensive program, including aerobic and strength physical training, kinesihydrotherapy and balance therapy, showed a more significant effect on the balance function after completion of the rehabilitation, rather than the standard rehabilitation method.

Keywords: obesity, kinesihydrotherapy, rehabilitation, stabilometry, balance

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EP519

The effectiveness of a comprehensive rehabilitation program including interactive balance therapy with biofeedback and kinesihydrotherapy in reducing body weight and changing the body composition in patients with obesity

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Objectives

To evaluate the effectiveness of a new comprehensive rehabilitation program on weight dynamics and body composition indicators using different methods after the rehabilitation stage and long-term results.

Material and methods

The Research includes men and women aged 40 to 65 with a body weight index more than 30 kg/m^2. Patients of the main group (Group 1) received 4 methods of physical therapy: balance therapy, group sessions of kinesihydrotherapy, group sessions with a special complex of therapeutic exercises in the hall, aerobic exercises on a bike or treadmill. Patients of the comparison group (group 2) were treated only with the use of aerobic exercises and therapeutic exercises in the hall according to the same methodology and with the same number of procedures as in the main group.

Results

According to the data obtained, in both groups, after the completion of the treatment phase, body weight significantly decreased in both groups, $P=0.0001$, waist circumference ($P=0.0001$ in group 1 and $P=0.005$ in group 2) and hip circumference ($P=0.0001$ in group 1 and $P=0.0003$ in group 2). In the main group, the thickness of the triceps fat fold decreased significantly ($P < 0.05$) after 14 days, 3 and 6 months, respectively (from 36.0 [28.0; 39.5] to 32.0 [24.0; 46 0] to 28.0 [20.5; 37.5] to 29.0 [19.0; 45.0] mm, respectively), the thickness of the abdominal fat fold decreased after 14 days, 3 and 6 months (from 67.5 [50.0; 77.5] to 56.0 [50.0; 68.0] to 46.0 [37.0; 50.0] to 50.0 [38.0; 70.0] mm, respectively. We received a significant ($P < 0.05$) decrease in fat mass according to bioimpedancemetry in the main group after 14 days and 3 months, respectively (from 65.7 [49.2; 72.1] to 60.9 [42. 2; 66.7] to 55.3 [39.3; 62.2] kg, respectively). In group 1, the decrease in adipose tissue according to the data of air-replacing body platysmography also significantly ($P < 0.05$) differed after 14 days, 3 months, respectively (from 56.8 [41.3; 77.5] to 49.7 [40.1; 57.1] to 44.4 [34.4; 64.4] kg, respectively).

Conclusions

The new complex program, including aerobic and strength physical training, kinesihydrotherapy and balance therapy in combination with a low-calorie diet, showed a more significant effect than the standard rehabilitation method on reducing body weight, reducing the thickness of fat folds, as well as changing the composition of the body, including 3 and 6 months follow-up.

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EP520

Prevalence of hirsutism in obese Tunisian women

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Introduction

Hirsutism is clinically defined as presence of excessive body hair in women in androgen-dependent areas. The aim of our study was to determine the prevalence and the characteristics of hirsutism in obesity.

Patients and methods

This was a descriptive cross-sectional study including 65 obese Tunisian women of reproductive age conducted in the obesity unit of the national Institute of nutrition of Tunis. The Ferriman-Gallwey score was used to evaluate hirsutism.

Results

The mean age of the patients was 33.36±10.76 years. The mean body mass index was 37.13±7.31 kg/m^{2}with morbid obesity in 32.3% of patients. The mean body fat percentage was 45.69±5.89% with a mean waist circumference of 110.43±21.86 cm. Diabetes, hypertension and dyslipidemia were found in respectively 23.1%, 16.9% and 15.4% of cases. The mean age at menarche was 11.94±2.46 years. Irregular menstrual cycles and amenorrhea was reported in respectively 28.1% and 17.5% of patients. Hirsutism was found in 41.5% of the patients: mild in 59.3% of cases, moderate in 7% and severe in 3.7% of cases. The mean blood testosterone level was 0.34±0.22 ng/ml [0.03–0.94]. Of the hirsute patients, blood testosterone level was below 0.6 ng/ml in 87.5% of cases and between 0.6 and 2 ng/ml for 3 patients. No patient had a testosteronemia above 2 ng/ml. Causes were dominated by polycystic ovary syndrome in 55.6% of cases.

Conclusion

Hirsutism is a frequent complication in obese women requiring a rigorous etiological investigation.

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EP521

Altered metabolism as a modified adolescent biomechanics component

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Obese teenagers are likely to become obese adults in the future. Obesity affects various bodily systems, including the musculoskeletal system, both biochemically and mechanically. These negative consequences are ultimately connected to wrongful muscle loading and unloading patterns. Pediatric obesity is especially dangerous. This study examined adolescents with BMI ranging from average weight to morbidly obese; various locomotion parameters were measured in adolescents. The study found numerous biomechanics parameters, including weight acceptance and push-off peak forces, stance time, and step length, were significantly modified in obese teenagers. The pattern of alterations suggests that muscular loading and unloading in obese adolescents changes to accommodate energy expenditure during locomotion. The study concludes by analyzing various metabolism changes that might contribute to the altered movement. Such adaptations, while seemingly allowing for locomotion adjustment in the short term, might perpetuate musculoskeletal and other systems pathologies if obese adolescents remain obese as adults.

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EP522

Iron deficiency anemia in pregnancy

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Introduction
Iron deficiency is common in pregnant women, and it causes an increased risk of premature delivery and fetal death. The aim of this study is to determine the prevalence of iron deficiency in pregnant women and find out the most common risk factors associated with anemia.
Methods
We performed a retrospective study on 52 pregnant women hospitalized in the c nutrition department. The definition of anemia as well as the objectives of the different parameters of the iron balance are retained referring to the recommendations of the world health organization.
Results
The age of our patients ranges between 21 and 36 years old. it was noted that 23% of women had a normal build before pregnancy 42% were overweight and 35% obese. Twenty-nine percent of patients were primiparous. The prevalence of anemia was 40%. Among them the anemia was mild in 76% and moderate in 24%. No severe anemia noted. The averages of hemoglobin and ferritin levels were respectively 10.26+- 1.21 g/dl and 18.23+-1.03 umol/l in anemic women and 12.34 g/dl, 33.81 umol/l in non-anemic women. Among anemic women 5% were in the 1st trimester 43% in the second trimester and 28% in the 3rd trimester. Ninety-five percent of women were symptomatic. The most common symptoms were: fatigue and dizziness in 67%, paleness and dyspnea in 62% and tachycardia in 57%. In our study a significant correlation was found between iron deficiency and personal history of prematurity ($r=0.301$, $P=0.03$), family history of anemia ($r=0.437$,$P=0.001$) and abandonment of menstruation ($r=0.301$, $P=0.03$). However, there were no significant differences with the parity of women ($r=0.082$, $P=0.566$), and the duration of menstruation ($r=-0.86$, $P=0.566$).
Conclusion
Screening for anemia in pregnant women is simple and essential to prevent its maternal and fetal consequences.

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EP523

Tissue-specific, adipose insulin resistance leads to hypertriglyceridemia

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Hypertriglyceridemia (HTG) is known to be a risk factor for cardiovascular diseases, such as atherosclerosis and hypertension. Although the association between insulin resistance (IR) and HTG has long been recognized, the causal relationship between them has not been elucidated yet. Proper understanding of the effect of IR on HTG may better start with the realization that IR implies much more than mere impairment of glucose uptake in tissues. Given that the role of insulin is widely different from tissue to tissue, metabolic disruptions due to IR would be very tissue-specific. Furthermore, IR would not necessarily develop simultaneously in the whole body but instead develop first predominantly in the muscle tissue with a low cell turnover and then progress to the adipose tissues and to the liver with higher cell turnovers. This may warrant that IR be subdivided better into tissue-specific IRs, such as the muscle insulin resistance (MIR), adipose insulin resistance (AIR), and hepatic insulin resistance (HIR). It is believed that HTG is related particularly with AIR. The AIR – failure of insulin action in adipose tissues – would not only impair glucose uptake into adipose tissues thereby elevating plasma glucose (PG) significantly, but also let adipose tissue lipases, such as hormone sensitive lipase (HSL) and adipose triglyceride lipase (ATGL), be inhibited not enough even in the fed state. Consequently, adipose tissues under AIR would not only undergo uninhibited lipolysis to release constantly fatty acids (FAs) into the plasma but also fail to entrap the fatty acids (FAs) released from the triglyceride-rich lipoproteins (TRLs), such as very low-density lipoproteins (VLDLs) and chylomicrons, that undergo, with the help of lipoprotein lipase (LPL), delipidation, which elevates severely the plasma fatty acid (PFA). Then, a significant fraction of severely elevated PFAs would also transport into the liver and subsequently, along with the FAs being released when the remnant TRLs taken up by the liver undergo hepatic breakdown, be formed into VLDLs and secreted back into the plasma, thereby contributing to severe elevation of plasma triglyceride (PTG), i.e., hypertriglyceridemia (HTG). As well known, chylomicrons of dietary fat origin delipidate much faster than VLDLs, which explains why VLDLs constitute the major component of PTG. In summary, AIR renders adipose tissues unable to esterify FAs into fats, which inevitably elevates PFA severely, which in turn enhances hepatic VLDL generation and secretin, thereby elevating PTG severely and thus leading to HTG.

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EP524

Biermer anemia in a type 2 diabetic not treated with Metformin

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Introduction
Anemia is defined by the World Health Organization as a hemoglobin concentration less than 120 g/l in women outside of pregnancy, and less than 130 g/l in men over 15 years of age. It is common in diabetics. It can be due to an autoimmune disease associated with type 1 diabetes, whereas the inflammatory cause is the primary cause in type 2 diabetes.
Observation
This is a 75 year old patient, type 2 diabetic for 21 years on insulin analogues without metformin; He presented with diabetic nephropathy and coronary insufficiency. In July 2022, the patient presented intense asthenia with anorexia and severe hypoglycemia of 0.3 g/l. In this context, a blood cell count was done showing anemia of 90 g/l with a mean blood volume of 109 fl. The etiological investigation confirmed a hypovitaminosis B12 with a normal folate level. The antiintrinsic factor antibodies were strongly positive. The diagnosis of Biermer anemia was retained and the patient was put on vitamin supplementation. Clinical and biological improvement and disappearance of hypoglycemia (assessment after one month of of vitamin B12 supplementation: hemoglobin 110 g/l with VGM 97 fl) were observed in our patient.
Conclusion
Beyond the search for a cause in order to ensure its treatment, the discovery of anemia in diabetic patients must systematically raise the question of its influence on glycemic control and the interpretation of glycated hemoglobin tests.

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EP525

The sociodemographic and metabolic factors associated with severe insulin resistance in individuals with type 2 diabetes mellitus

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Some patients with type 2 diabetes mellitus (T2DM) suffer from severe acquired insulin resistance (IR). There is still a shortage of research analyzing the T2DM patients with severe IR and identifying their risk factors.
Aim
To evaluate how selected sociodemographic and metabolic factors are linked to severe IR among patients with T2DM.
Methods
It was a case control study. If T2DM patients received high insulin doses (> 1 IU/kg/day) and their HbA1c $\geq$ 9%, they were assigned to the case group ($n=58$). Patients with lower insulin requirements (< 1 IU/kg per day) and HbA1c

$< 8\%$ were assigned to the control group ($n=62$). Participants of control group were matched by gender and BMI with the case group. Data was analyzed using SPSS 27.0 software. The level of statistical significance was set as $P < 0.05$.
Results
The data of 120 patients with T2DM was analyzed (Table 1and Table 2).
Conclusions
1. T2DM patients with severe insulin resistance (case group) were younger and their diabetes duration was shorter compared to the control group.
2. The case group subjects had a higher prevalence of metabolic syndrome and dyslipidemia itself, exclusively hypertriglyceridemia.

Table 1 Clinical characteristics of participants and the control group.

Variable	Case group (severe IR) $n=62$	Control group (unexpressed IR) $n=58$	P value
Gender (male/female), %	48.3 / 51.7	40.3 / 59.7	NS
BMI (kg/m^2), m± s.d.	36.35±5.75	34.07±6.94	NS
Age (years), m± s.d.	61.10±9.48	67.85±8.51	<0.001
HbA1c (%), m± s.d.	10.36±1.11	6.89±0.82	<0.001
Duration of DM (years), m± s.d.	16.1±7.47	19.4±8.40	<0.001
Education (high (university) /middle), %	27.6/72.4	23.3/76.7	NS
Marital status (married/single), %	60.3/39.7	56.7/43.3	NS
Median of C-peptide (ng/ml), min-max	0.43 (0.01–1.84)	0.44 (0.01–2.44)	NS
Daily insulin dose (IU/d), median, min–max	149 (108–252)	60 (16–125)	<0.001

NS - non-significant difference

Table 2 The evaluation of metabolic parameters in the case and control groups.

Variable	Case group, $n=62$	Control group, $n=58$	P value
Dyslipidemia (no/yes), %	13.8/86.2	32.2/67.8	0.018
Total cholesterol, mmol/l (m± s.d.)	5.54±2.14	5.1±1.49	NS
HDL, mmol/l (median, min–max)	1.07 (0.54–5.55)	1.1 (0.48–3.29)	NS
LDL, mmol/l (median ± s.d.)	3.12±1.28	3.23±1.08	NS
Triglycerides, mmol/l (median, min–max)	3.03 (0.8–18.8)	1.35 (0.49–4.49)	<0.001
Metabolic syndrome (yes), n (%)	49 (84.4)	37 (61.7)	0.005

NS – non-significant difference

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EP526

GAZA study (Glycémie Améliorée Zéro Antidiabétique), a new antidiabetic therapeutic approach without pharmacoligical treatment

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Introduction
In diabetology all the recommendations insist on the intensification of the antidiabetic treatment with the maintenance of the same treatment if the type 2 diabetes mellitus is balanced. Our work insists on dietary treatment and focuses on weight loss in order to degress antidiabetic treatment until cessation.
Patients and methods
This is a prospective interventional study. Type 2 diabetes mellitus on pharmacological treatment: treatment is reduced if HbA1c $\leq$ 6.5%, until treatment is stopped in order to integrate the study. Type 2 diabetes mellitus without pharmacological treatment are monitored quarterly for 24 months, based on weight, fasting blood sugar and HbA1c.
Results
Our work brought together 289 patients with a sex ratio of 0.85 and an average age of 52 years and an average BMI of 29.6 kg/m^2, the average duration under antidiabetic treatment is 15 months, 74% under mono or dual therapy, 4 patients on insulin. 4% refused to stop treatment, 20% failed to stop treatment, 71% are still without pharmacological treatment, of which 49% exceeded 12 months and 20% exceeded 24 months. During the 24 months of follow-up: the average weight loss compared to the initial weight varied between −3 kg and −4.4 kg, the average fasting blood sugar varied between 1.10 and 1.19 g/l and HbA1c varied between 6.1% and 6.4%
Conclusion
As the intensification of the antidiabetic treatment is essential in the management of the patients with type 2 diabetes mellitus, the degression must be integrated into the therapeutic strategy in order to preserve the pancreatic capital and ensure a better quality of life.

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EP527

Diabetes and Ramadan, special Ramadan blood glucose self-monitoring table

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Background
International Diabetes Federation (IDF), in collaboration with the Diabetes and Ramadan (DAR) International Alliance proposed in 2021, IDF-DAR Practical Guidelines with a score that allows certain patients even on insulin to fast which requires regular and appropriate blood glucose monitoring.
Aim
Develop a special Ramadan blood glucose self-monitoring table in order to limit the risk of acute compilations during this month.
Method
Our work is a literature review and analysis of the pharmacokinetics of antidiabetics in order to determine the critical moments during Ramadan. It should be noted that, IFTAR: evening meal, SUHOOR: dawn meal.
Results
Our table contains 5 columns: Pre-SUHOOR, post-SUHOOR, at 1600 hours (frequent moment of hypoglycemia), Pre-IFTAR, post-IFTAR (Table 1A/ Non-insulin antidiabetics: the essential moments are: 1/ post-SUHOOR: to find out if the patient can continue fasting. 2/ at 1600 hours: the most critical period for hypoglycemia. 3/ post-IFTAR to correct dietary deviations in the event of hyperglycemia, and readjust the doses of antidiabetics in the event of hypoglycemia. B/ Basal insulin: will be readjusted according to blood glucose at 1600 hours and Pre-IFTAR. C/ short-acting insulin: the dose of IFTAR will be readjusted according to the blood glucose level post-IFTAR, the dose of SUHOOR will be readjusted according to the blood glucose post-SUHOOR. D/ Premixed insulin: the dose of IFTAR will be readjusted according to the blood glucose level post-IFTAR and Pre-SUHOOR, the dose of SUHOOR will be readjusted according to the blood glucose post-SUHOOR, at 1600 hours and Pre-IFTAR.
Conclusion
Fasting during Ramadan constitutes a major risk for diabetic patients, appropriate and regular blood glucose self-monitoring can help diabetics to manage treatment and diet well.

Table 1

Pre-Suhoor		Post-Suhoor	1600 hours	Pre-Iftar	Post-Iftar		
Blood Glucose	Short acting/ premixed insulin	Blood Glucose	Blood Glucose	Blood Glucose	Short acting/ premixed insulin	Blood Glucose	Basal insulin

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EP528

The effect of hypoglycemic therapy on functional state of the kidneys in patients with type 2 diabetes mellitus

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The purpose of the study was to assess the functional state of the kidneys in patients with type 2 diabetes, depending on hypoglycemic therapy.
Material and research methods
60 patients with type 2 diabetes with CKD. The mean age of the patients was 54± 2.5 years, the experience of diabetes was 11.7±0.18, the mean Hb1C was 9.1%, and the mean fasting glycemia was 11.2 mmol/l. The patients were divided into 2 groups: group 1-30 patients on the iSGLT-2+ metformin, group 2–30 patients on the iDPP-4+metformin. The observation period was 6 months.

Research results and discussion
In patients with type 2 diabetes with diabetic nephropathy (CKD 2,A2), iSGLT 2 after 6 months of observation effectively reduced the level of glycated hemoglobin (Hb1C) by 1.0% and fasting plasma glucose was 8.4 mmol/l, in patients taking iDPP-4 10 mmol/l. A significant improvement in GFR is observed after 6 months of taking iSGLT-2, at the 1st visit 69.2 ± 0.08 ml/min per 1.7 m^2 after 6 months 82.7 ± 2.85 ml/min per 1.7 m^2. According to our results, IGLT2 reduces the risk of progression of albuminuria, 68% of patients reported MAU – 32.01 mg/day at the 1st visit, after 6 months 28.5 mg/day.
Conclusions
The use of iSGLT-2 in DM2 patients with nephropathy not only improves glycemic control and slows down the development of diabetic kidney damage (reduces the rate of increase in albuminuria and improves GFR).

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EP529

The efficacy of regimens for sodium-glucose countertranspoter 2 inhibitor (Emaglyf) with metformin and DPP-4 inhibitor (Januvia) in patients with DM 2 and stage 1-3 chronic kidney disease

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Aim of the study
To study the effectiveness of combination therapy of sodium-glucose countertranspoter 2 inhibitor -SGLT-2 – (Emaglyf) with metformin and DPP-4 inhibitor (Januvia) in patients with stage 1–3 chronic kidney disease associated with DM 2.
Material and research methods
A total of 40 patients with type 2 diabetes and CKD grades 1–4 were selected. To study the effect of various schemes of nephroprotective therapy on the functional state of the kidneys in DM 2, patients were divided into 2 therapeutic groups: Group 1 consisted of 20 patients with DM 2 and CKD 1–3 tbsp. receivingSGLT-2 (emoglyph) + metformin Group 2 consisted of 20 patients with DM 2 and CKD 1–3 tbsp. receivingSGLT-2 (Emoglyph) + DPP 4 (Januvia). In the work, general clinical, clinical and biochemical (AL, AST, bilirubin, PTI, urea, creatinine, GFR, C-reactive protein, etc.), hormonal (insulin, C-peptide), immunological (uromodulin) methods of blood tests, as well as instrumental methods of examination – ultrasound of internal organs, Ultrasound and dopplerography of renal vessels, as well as statistical methods. We also evaluated the results of ECG in 12 conventional leads and echocardiography (EchoCG) (dimensions of the chambers of the heart, the thickness of its walls and myocardial contractility). The control group consisted of 20 healthy individuals.
Research results
The initial data of carbohydrate metabolism indicated its decompensation in the studied groups. There were no significant differences between the Doppler values of the renal arteries in the groups. At the same time, the indicators significantly differed from those of the control group.
Conclusions
1) After 6 months of therapy, the indicators of carbohydrate metabolism reached normalization in both groups, while the best results were observed when using the SGLT-2+ DPP4 regimen
2) After 6 months of treatment, significant differences were found between the Doppler values of the renal arteries in the groups, namely, when using the SGLT-2+ DPP4 scheme

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EP530

Diabetic osteoarthropathy: A case report

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Introduction
Diabetic osteoarthropathy (D.O) commonly referred to as Charcot's foot is a complication secondary to neuropathic and inflammatory osteolysis, occurring in a setting of old and/or poorly controlled diabetes. Its pathophysiology remains poorly understood and its diagnosis must be systematically evoked in the presence of any inflammatory sign that localised to the foot or ankle occurring on a background of diabetic neuropathy.
Clinical case
Sixty four year-old female patient, diabetic since the age of 48 years on 2 premixed and rapid analogue. Her diabetes was unbalanced and she was already at the stage of degenerative complications, with the notion of amputation of the 3rd toe of the right foot following gangrene. The patient was admitted with pain in the left foot that had been evolving for 5 months, occurring in the context of prolonged walking and without any notion of trauma. Clinically, the foot was deformed, painful, with enlargement of its anteroposterior and lateromedial diameter. Biological tests revealed a high CRP and LDH without hyperleukocytosis. An X-ray of the left foot showed secondary ossifications with marginal sclerosis and exostoses. A CT scan showed hypertrophy and destruction of the bone with infiltration of the periarticular soft tissues in favour of a Charcot foot. The left foot was immobilised in a plaster cast and offloaded with the patient being put on a progressive dose of pregabalin with improvement of her pain.
Discussion
Currently diabetes is the leading cause of diabetic osteoarthropathy. Unilaterality of the disease is dominant. Intense bone demineralisation is evidence of significant autonomic damage. Our patient had a delay in diagnosis which could be explained in part by the rarity of this pathological entity and the lack of specificity of its clinical picture. The cornerstone of management is an early clinical and radiological diagnosis strict unloading of the foot, appropriate analgesia with a careful discussion of the surgical indication in the state phase in order to prevent the development of ulcerations, a major cause of amputation.
Conclusion
D.O is often under-diagnosed due to the non specificity of the clinicobiological picture. It is characterised by irreversible osteoarticular complications, hence the importance of early diagnosis with adequate management based on offloading and early immobilisation in parallel with good therapeutic education.
Key words: diabetes-osteorthropathy-unloading-surgery.

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EP531

Emphysematous cystitis in diabetics

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Introduction
Emphysematous cystitis is a rare rare condition encountered mainly in poorly balanced diabetic patients. It represents a rare cause of septic shock and is characterized by the presence of air in the wall and/or the bladder lumen. Abdominopelvic computed tomography remains the key examination to confirm the diagnosis.
Observation
We report the case of a 65-year-old patient with a history of non-ill-controlled type 2 diabetes on sulfonylureas and complicated by diabetic retinopathy and diabetic neuropathy. He was admitted for management of a glycemic imbalance associated with urinary burning and vomiting. Clinical examination found pelvic tenderness. The balance shows neutrophilic polymorphonuclear leukocytosis with white blood cells at 11550/ul and a CRP at 24.8 mg/l. He has unbalanced diabetes (HBA1C = 9%) and functional renal failure (creatinine = 76.13 mg/l). Thoraco-abdomino-pelvic CT demonstrates emphysematous cystitis. The evolution is favorable under antibiotic therapy, insulin therapy and bladder drainage.
Conclusion
Urinary tract infections are more frequent and more serious in diabetic patients. They can have a severe prognosis, hence the need for early diagnosis and rapid treatment.

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EP532

Pregnancy after exposure to GLP-1 receptor agonists. A case report and literature review

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GLP-1 receptor agonists have become an important group of drugs used in the treatment of type 2 diabetes and then obesity. There are also many reports of very beneficial effects, e.g. in the treatment of polycystic ovary syndrome.

Multidirectional metabolic impact, weight loss, menstrual regularity, and therefore fertility, when used in a group of young women, the possibility of pregnancy should always be taken. We present a case report of the patient which is the starting point for a review of the current state of the art, a review of the literature, and the proposed management of GLP-11 analogs treatment among women of reproductive age. A 43-year-old patient with type 2 diabetes treated with metformin and semaglutide in the fifth pregnancy, in the seventh week of pregnancy, came to a gynecologist and diabetologist, which meant several weeks of exposure to semaglutide in the first trimester of pregnancy. In the obstetric history – 2 deliveries and 2 miscarriages, history of irregular menstruation. A patient with a diagnosis of diabetes in pregnancy during a second pregnancy, was treated with metformin after delivery, and then semaglutide was added. Semglutide for 6 months. The patient did not use oral contraception, because she planned the implantation of intrauterine device. Glycated hemoglobin was 5.4%. Semaglutide was discontinued and the patient quickly required the functional insulin therapy. The reference ultrasound examinations of the first and second trimesters did not reveal any fetal defects. In subsequent trimesters, HBA1c-5.2–5.4%. The girl The fetus was through a transverse incision in the lower uterine segment. The fetus was a female delivered at 35 gestational age, weighing 2750 g. GLP-1 agonists have been classified by the FDA and EMA as group C, which means that they are contraindicated during pregnancy. From preclinical studies, we know about skeletal defects in rodents and rabbits. There is a recommendation to use contraception in the pre-pregnancy women and a time of wash-out recommendation. For semglutide it is- 2 months. There are only single cases describing pregnancy during exposure to GLP-1RA. Most likely, in the coming years the data will be more accurate because the increasing use of GLP-1 receptor agonists in treatment provide data in cases of unplaned pregnancies. We will also need a long-term observation of those patients and their offspring.

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EP533

Hyperhomocysteinemia in post-covid diabetic patients in Adjara Region, Georgia (Country)

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Objective
Post Covid Syndrom (PCS) after Covid Pamdemic is a major couse of morbidity for Diabetic patients. In the last 30 years, a new metabolic risk factor for vascular damage – hyperhomocysteinemia (HtHcy) has been identified and is considered as an independent risk factor for the development of cardiovascular pathologies and the possible lethal outcome.
Aim of study
This study was undertaken to check association of plasma Hcy level in post covid diabetics with increased risk of CVD. That's why, due to the growing number of patients with T2DM with Long Covid symptoms and complications we decided to study non-insulin-dependent diabetics in this area to determine the correlation between Covid infection and HtHcy and give some evidence about correlation between CVD high risk.
Keywords: homocysteine; Post Covid Syndrome (Pcs), plasma, type 2 diabetes mellitus, cardiovascular disease CVD.
Method and design
Case-control study, was conducted to assess the effect on plasma homocysteine (Hcy) in 74 type 2 diabetic out-patients with anamnesis of Covid 19 only who did not require hospitalization for COVID-19 disease were included this study. Clinical data and laboratory results of 74 RT-PCR-positive COVID-19 cases were collected, aged between 65 > years old man and woman, ambulatory visited 6 endocrinologist and 3 cardiologists in 3 primary care clinic, city Batumi, period between March 10 – to November 23, 2022. 34 of these patients had a history of cardiovascular complication, or Heart Bypass Surgery CABG(7 pts) before Covid-19 disease. Test results of metabolite panel: B12, folate and homocysteine, which were run in the immunochemistry module of Cobas®8000 analyzer using Electro Chemi Luminescence technology (Roche diagnostics, Mannheim, Germany).
Results
74 Post COVID-19 diabetic patients (43 males, 31 females) were enrolled in the study. Laboratory results: Homocysteine (μmol/l) – 15.62±1.37; Folate (mg/l) – 4.59±0.41; B12 (ng/l) –531.50±62.20.
Summery points
Hyperhomocysteinemia was observed in post COVID diabetic patients included in the study; We recommend analysis of homocysteine levels to predict the course of the post Covid syndrome; Homocysteine levels in post COVID-19 NIDDM patients can be evaluated for a predictive, preventive and personalized medical approach.
Conclusion
Homocysteine levels can be used as a prognostic parameter that can predict the severity of post COVID-19 disease. We believe that studies on disease severity and predictive medicine in the field of biomarkers will increase in the future.
Competing interests: Authors state no conflict of interest.

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EP534

Metabolic profile and clinical hyperandrogenism in Cushing's disease

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Introduction
Cushing's disease is a rare condition that represents the most common cause of endogenous Cushing's syndrome. Its severity is due to cardiovascular complications, with high morbi-mortality rates. This study aims to evaluate the specific features of metabolic disorders in females having Cushing's disease and presenting a clinical hyperandrogenism.
Materials and methods
Retrospective and descriptive study, including 12 female patients with Cushing's disease presenting a clinical hyperandrogenism, recruited in the Endocrinology-Diabetology-Nutrition department of university hospital center Mohammed VI of Oujda between 2016 and 2022. Statistical analysis was performed by SPSS version 21 software.
Results
The mean age was 30.3±11.8 years, with age ranging from 14 to 54 years. The average BMI was 32.7±8.1 kg/m^2, obesity was observed in 41.6% of our patients. The mean waist circumference was 107.4±13 cm. Dyslipidemia was found in 66.7% of patients: mixed dislipidemia was noted in 58.3% of them, hypercholesterolemia was found in 91.6% and hypoHDLemia was described in 83.3% of cases. In addition 33.3% of our patients were diabetics with a mean HBA1c of 6.5±1.3%, requiring insulin therapy in 50% and metformin in monotherapy in 50% of cases. Twenty-five percent of our patients had an association of diabetes and arteriel hypertension. In total, 58.3% of our patients had a metabolic syndrome.
Discussion-conclusion
In Cushing's disease, hypercortisolism leads, through a combination of effects on the liver, muscles, adipose tissue and pancreas, to an augmentation of gluconeogenesis and an alteration of insulin sensitivity, causing glucidic metabolism disorders. The therapeutic approach to these patients must be comprehensive, including the control of associated cardiometabolic diseases, in order to reduce morbidity and mortality rates. (1)
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EP535

Parathyroid hormone level in people on programmed hemodialysis

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Introduction
The purpose of this work was monitor the frequency of determination and compare the levels of parathyroid hormone in blood plasma in people on programmed hemodialysis.
Material and methods
Data from medical records of 465 patients on programmed hemodialysis who were admitted to the Republican Centre of Nephrology and Kidney Transplantation were analyzed. Patients according to reason of end stage of renal failure were divided into 3 groups due to chronic glomerulonephritis, diabetes mellitus and other reasons.

Results
The level of glycemia was significantly higher in the group of patients with DM, the level of creatinine, urea nitrogen, calcium, phosphorus in the blood plasma was high and no differences were found between the groups. Only 15% patients on Programmed hemodialysis PTH level in blood plasma, while 48% of them have a normal range and 52% have a higher levels of hormone.
Conclusion
Determination of the PTH level in blood plasma and early diagnosis of hyperparathyroidism in people on programmed hemodialysis were performed at an insufficient level in our study. Eliminating this fault will undoubtedly help to improve the effect of treatment and increase the life expectancy of patients.

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EP536

Increased Visceral to Subcutaneous Fat Ratio is the Key to Type 2 Diabetes Pathogenesis and Treatment: New Hypothesis

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Introduction
Many researchers are linking diabetes with obesity, which has become very prevalent now, but we see large numbers of diabetics with normal weight as we see obese persons, but they are not necessarily diabetics, which calls us seriously to review this matter, taking into account that obesity is a factor in the occurrence of diabetes. Many studies have talked about visceral fat, as well as about the ratio between visceral fat and subcutaneous fat and its role in the occurrence of insulin resistance and diabetes. Here, we consider that the increase in the percentage of visceral fat, that is, the fat that is not in its right place, is an important indicator of the occurrence of this major defect in the metabolism process, which represents severe stress on the genes responsible for the metabolism process and represents severe stress on the beta cells in the pancreas.
Materials and methods
600 patients followed in a private clinic in observational prospective study. Patients have been categorized into 6 groups according to being diabetic, prediabetic, control, with normal body mass index or high body mass index.
Results
The results exhibit a statistically notable difference between overweight diabetic patients and overweight control as regards increased visceral fat to subcutaneous fat ratio with *P* value less than 0.0001. The results exhibit a statistically notable difference between overweight prediabetic patients and overweight control as regards increased visceral fat to subcutaneous fat ratio with *P* value less than 0.0001. The results exhibit a statistically notable difference between normal weight diabetic patients and normal weight control as regards increased visceral fat to subcutaneous fat ratio with *P* value less than 0.0001. The results exhibit a statistically notable difference between normal weight prediabetic patients and normal weight control as regards increased visceral fat to subcutaneous fat ratio with *P* value less than 0.0001. Most patients with diabetes and prediabetic have visceral to subcutaneous fat ratio more than 0.6 which can be considered as a cutoff point to type 2 diabetes mellitus diagnosis.
Conclusion
As type 2 diabetes grows in an epidemic way, it is a must to know the pathogenesis and find new treatment pathways. Epigenetics explain most of type 2 diabetes cases by increasing visceral to subcutaneous fat ratio.
Keywords: type 2 diabetes, visceral fat, subcutaneous fat, and epigenetics.

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EP537

Keto-acidosis decompensation and centropontic myelinolysis: incidental finding-a case report

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Introduction
Centropontic myelinolysis (CPM) is a neurological pathology related to axonal demyelination lesions, often localized at the pontine level. For a long time, this condition was attributed to rapid correction of hyponatremia. A few cases of PCM with normal natraemia have been described, in a context of undernutrition, chronic alcoholism, hypokalaemia or hyperglycaemia.
Patient and observation
We report the case of an 18 years old patient, type 1 diabetic for 8 years, admitted for keto-asidosis decompensation. On admission, the patient was conscious, hemodynamically and respiratorily stable, capillary blood glucose was elevated to 6 g/l, with the presence of 3 crosses of acetone and sugar on urine dipstick. The biological workup showed a venous glucose level of 6.16 g/l, a corrected natraemia of 137 mmol/l, a kalemia of 3.7 mmol/l, and low alkaline reserves of 13 meq/l. The emergency was resolved and the patient underwent a thorough clinical examination, which revealed FTT severe staturo-ponderal delay, a micro penis and bilateral paresthesias in all 4 limbs. A hypothalamic-pituitary MRI in search of a central cause of FTT was performed, showing the presence of a pontine lesion suggestive of PCM.
Discussion
PCM was first described in 1959. Microscopically, it is a symmetrical destruction of myelin involving all nerve bundles associated with a loss of oligodendrocytes. Often, it has been attributed to a rapid correction of hyponatremia. In the case of normal natraemia, it can be hypothesized that rapid elevation of blood glucose has the same effect as a rapid infusion of hypertonic saline. MRI remains the imaging technique of choice. An effective but slow correction of the blood sugar level allows a good evolution of the clinical picture.

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Morphofunctional assessment of nutritional status in patients with type 1 diabetes mellitus

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Objective
To evaluate the nutritional status in patients with type 1 diabetes mellitus (DM1) or latent autoimmune diabetes in adults (LADA).
Methods
Observational transversal clinical study in patients with DM1/LADA. Nutritional assessment was performed using bioelectrical impedance analysis (BIA), dynamometry, ultrasound of rectus femoris muscle and subcutaneous fat tissue, functional tests and laboratory parameters. Statistical analysis was performed with SPSS v.25.
Results
In our cohort, thirty-nine males were included. Mean age: 51.5 ± 13.3 years, with a mean DM evolution time of 22.2 ± 14.7 years. The prevalence of microvascular or macrovascular complications were 66.7%. 30.8% and 61.5% of the patients had high and very high cardiovascular risk, respectively. Mean BMI: 26.8 ± 3.9 kg/m2. 66.7% of patients were overweight or obese. According to the GLIM criteria, 3 patients, aged over than 60 years and with other comorbidities, were classified as malnourished. Mean value of body cell mass (BCMe) measured by bioelectrical impedance was 40.5 ± 5.3%. 35.1% of patients presented decreased standardized phase angle (SPA) (Mean 5.8 ± 1.35°). Mean lean mass: 72.8 ± 12.5%. Mean fat mass: 21.5 ± 7.4%. Mean calf circumference: 37.5 ± 3.8 cm. 12.8% had decreased hand dynamometry values (according to references values by aged groups) and the mean of the Up and Go test was 8.9 ± 2.2 seconds. In our cohort, there were not altered serum nutritional parameters. Mean value of adipose tissue thickness in rectus femoris (measured by ultrasound) was 0.8 ± 0.3 cm, with a median circumference of 9.5 ± 1.5 cm and an area of 7.1 cm^2. Abdominal adipose tissue ultrasound revealed a total thickness of 2.5 ± 0.9 cm, the median values were: superficial adipose tissue 0.69 ± 0.31 cm, deep adipose tissue 0.86 ± 0.40 cm and preperitoneal adipose tissue 0.89 ± 0.69 cm.
Conclusion
The role of morphofunctional assessment of nutritional status in the follow-up of patients with DM1/LADA is not fully established. It is necessary to continue the study of the application in daily clinical practice of emerging techniques such us nutritional ultrasound in these patients.

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False informations about diabetes in arabic speaking YouTube Videos

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Introduction
Nowadays, social media has become a valuable source of health-related information which can have an important impact on people's behaviors and

decisions regarding their diseases. To improve management of diabetes, patients often seek health information in social media platforms, including Youtube. However, the nature of its content, which anyone can upload, isn't always reliable and scientifically accurate, sometimes even misleading. The aim of this study is to analyse false informations in diabetes related youtube videos.
Methods
A YouTube query using the *search* terms "diabetes treatment" in arab language was performed at the date of January 17th 2023. The most viewed 50 videos which first appeared in the search results were included in the analysis. We assessed the veracity of informations contained in every video. The nature, publisher, and supposed aim of false informations was noted.
Results
The percentage of videos containing false informations was 63% of the total; The titles contained 75% and the "poster" 75% of misleading data. 77% of the videos were published by profiles presenting themselves as doctors. The topics containing the highest percentage of false infomaiotns were alternativs medicine (100%), dietetics (76%), Treatement (72%) and pathophysiology of type 2 diabetes (52%). 37% of the videos contained religious content, 63% encouraged diabetics to stop their medications. 49% of the posters declared negative opinions about the medical community, and the same percentage had anti-conspiracy opinions.
Conclusion
False and misleading informations are widespread in Arabic speaking diabetes related videos of youtube. Patient education should therefore include awareness that this social media should not be considered a reliable source of diabetes information and management.

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Assessment of metabolic profile in type 2 diabetic patients after 12 weeks of treatment by Liraglutide

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Introduction
Liraglutide has been shown to have a positive effect on the glycemic and lipidic profile of diabetic patients. We aimed to assess the metabolic profile in type 2 diabetic patients after 12 weeks of treatment by Liraglutide
Methods
This is a prospective study performed at the endocrinology department of the Military Hospital of Tunis. We recruited 22 patients with type 2 diabetes (T2D) treated with insulin and/or oral antidiabetics. Liraglutide 1.2 mg was initiated subcutaneously once daily for 12 weeks to these patients. Anthropometric parameters and blood samples were collected at 0 and 12 weeks.
Results
The study population consisted of 8 male and 14 female individuals, with a mean age of 53.8 years with extremes ranging from 32 years to 66 years.. All of the patients had a body mass index indicative of overweight status, with 20 obese patients. Eight patients had hyperlipidemia, fifteen patients had hypertension and seven patients had coronary artery disease. There was no significant reduction in weight (110.7 kg vs 110.3 kg, $P=0.639$) but the reduction of body fat percentage was significant (40.7% vs 38.4%, $P=0.046$). HbA1c was significantly reduced at 12 weeks with Liraglutide (9.7% vs 8.4% $P=0.022$) but there were no significant reduction in fasting plasma glucose (12.2 vs 10.2 mmol/l, $P=0.113$). Regarding the lipidic profile, there was no significant modification in total cholesterol (4.5 vs 4.3 mmol/l, $P=0.318$), LDL cholesterol (2.41 vs 2.28 mmol/l,, $P=0.569$), Triglycerides (2.4 vs 2.3 mmol/l, $P=0.835$) and HDL cholesterol (1.1 vs 1.1 mmol/l, $P=0.71$).
Conclusion
Studies have shown that treatment with Liraglutide can lead to significant weight loss, reduction in HbA1c levels and decrease in total cholesterol, LDL cholesterol and triglycerides, which are all markers of cardiovascular risk. Liraglutide also increases HDL cholesterol. Our study supports these results in terms of glycemic control, but we did not find an improvement in the lipid profile. A study with a larger sample size is needed.

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Insulin intolerance: Adipose panniculitis

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Introduction
Besides insulin allergy, several other forms of insulin intolerance are possible. Adipose panniculitis (AP) is an acute form.
Purpose
Describe the clinical, paraclinical and evolution of AP.
Clinical case
64-year-old patient, type 2 diabetic for 24 years on premixed human insulin for 10 years. He consults for itchy erythematous lesions at the insulin injection sites. The lesion begins with an immediate pruritus then appearance a few hours later of a local inflammation which increases in diameter. The examination finds an induration of 10 cm in diameter of necrotic aspect with improvement under topical corticosteroids. Several types of human insulin and analogues have been used. We eliminated an allergy to protamine, metacresol and zinc. likewise, dermographism has been eliminated. The pharmacovigilance investigation incriminated INSULATARD, ACTRAPID, APIDRA and LANTUS. Skin biopsy showed fatty panniculitis. The management was to put the patient on Lantus and Apidra with dose splitting on different sites. The evolution was favorable.
Discussion
Manifestations of insulin intolerance can occur several weeks, months or sometimes years after the start of insulin therapy. The time to onset of symptoms was very suggestive of drug origin. The evolution when the injections were stopped was marked by a regression of the inflammatory signs. Re-administrations at other sites reproduced the same lesions. It is an inflammatory panniculitis compatible with type III delayed hypersensitivity. For our patient: favorable evolution under fractionated LANTUS + APIDRA with topical corticosteroid.
Conclusion
Insulin allergy requires prompt diagnosis and management to ensure safe glycemic control.

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Hospitalization of diabetic patients: What impact on their metabolic profile?

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Introduction
Persons with diabetes may need to be hospitalized in order to improve diabetes balance. We aimed to evaluate the benefits from hospitalization in a diabetes department on glycemic parameters.
Method
It was a descriptive cross-sectional study conducted on diabetic patients consulting for the first time after a hospitalization in the department (C) of the National Institute of Nutrition of Tunis for the management of a poorly controlled diabetes.
Results
We included 60 diabetic patients with a mean age of 49.1 ± 16.8 years and a sex ratio (M/F) of 0.28. Type 2 diabetes affected 66% of the patients. The mean body mass index increased from 28.2 ± 5.9 kg/m^2 during hospitalization to 29 ± 5.7 kg/m^2 at the follow-up visit ($P=$NS). The mean fasting blood glucose remained stable: 11.6 mmol/l during hospitalization VS 11.2 mmol/l at the consultation while glycated haemoglobin decreased significantly from 10.2% to 9.1% ($P=0.009$). The lipid profile showed a non-significant decrease in triglyceride levels from 1.6 mmol/l to 1.4 mmol/l, a non-significant increase in total cholesterol levels from 4.5 mmol/l to 5 mmol/l.
Conclusion
Therapeutic and dietary education is a pillar of care for all hospitalized diabetic patients to achieve good glycemic control while maintaining regular outpatient monitoring.

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Association of ABO blood groups with diabetic microvascular complications

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Background
Micro vascular complications are the major outcome of Type 2 Diabetes Mellitus progression, which reduces the quality of life and increases diabetic morbidity & mortality. As the incidence of type 2 diabetes is growing day by day; our search for its aetiology and pathogenesis is also ever growing to predict its risk factors and early screening for better care and prevention of its complications. Many studies have tried to link susceptibility of type 2 diabetes with ABO blood group though results have been inconsistent. The present study aims to analyse association of micro vascular complication with different blood groups if any.
Methods
The study included the paitents with diabetes who were hospitalized and followed up in our clinic form Dec. 2019 to April 2022. Information such as age, sex, and family history of diabetes was scanned from medical records. The blood group was determined by standard serological methods. Screening of microvascular complications done by appropriate clinical examinations and laboratory investigations.
Results
There was 348 patients with type 2 diabetesin this study, the average age of the patients was 59.3±12.8, male to female ratio was 142(40.8%)/204 (59.8%) reapectively. 246 (70.68%) patients had one or the other complications. Diabetic nephropathy, rethinopathy and neuropathy ratio was 31.3%, 35.20% ve %52.0% respectively. None of the type of micro vascular complication was found to be significantly associated with different blood groups. In addition we found that Rh (−) group had significantly low Diabetic nephropathy, rethinopathy compare to Rh (+) group ($P=0.044$ ve P 0.041).
Conclusions
Although we didn't finde a relationship between ABO blood group and diabetic microvascular complications, Rh (+) was found to be a risk factor for developing nephropathy and retinopathy.

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Diabetes health promotion self-care scale: Reliability and validity of the Turkish Version

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This study was carried out to put the Diabetes Health Promotion Self-Care Scale for patients with Type 2 diabetes mellitus (DM) into use for nursing and medical literature. The sample of this methodological design research consisted of 620 patients diagnosed with type 2 DM. The data were collected with Personal Information Form and the Diabetes Health Promotion Self-Care Scale. In the validity and reliability stage of the scale, exploratory and confirmatory factor analyzes, and structural equation modeling was used for the item analyzes, internal consistency, and structural validity. The statistical analysis showed that the reliability coefficient of the scale was Cronbach $\alpha=0.922$. The sub-factors of the Diabetes Health Promotion Self-Care Scale consisting of 27 items and 7 sub-factors were determined as 'Interpersonal Relationships', 'Blood glucose self-monitoring', 'Personal Health Responsibility', 'Exercise', 'Diet', 'Adherence to the Recommended Regime', and 'Foot Care'. As a result of the analysis, the Diabetes Health Promotion Self-Care Scale was found as a valid and reliable scale to be applied to Turkish society.

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The activation value of the renin-angiotensin-aldosterone system in the pathogenesis of late complications of DM 2

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Aim
To study the indicators of RAAS in patients with DM 2 with chronic heart failure (CHF) and diabetic foot syndrome (DFS).
Material and methods
We observed 75 patients with DM 2, CHF and DFS. Patients were distributed into 3 groups: 1 gr – patients with 2 t and neuroichemic form of DFS and CHF – 22 patients, 2 groups – patients with DM 2 and neuroichemic form of DFS without CHF – 28 patients, 3 groups – patients with CHF without DM 2 –25 patients Patients performed general clinical, biochemical, hormonal, genetic blood tests, as well as an ECG, Echo-ECG, etc. Instrumental studies, as well as statistical methods.
Results
In the study of aldosterone, its increased average values were found in all groups. In patients with CHF, the indicators are reliable than in the group of patients with DM 2. In the group of patients with DM 2 in combination with CHF, the indicators were the highest, reliably different from the indicators of patients with diabetes and unreliable in comparison with the CHF group. Renin levels in groups were significantly higher than the upper limit of the norm lying. However, it should be noted that in the DM 2+CHF group, indicators statistically reliably exceeded the indicators in the first two groups.
Conclusions
Chronic hyperglycemia and RAAS activation are pathogenetic factors that aggravate the course of CHF in patients with DM2. This, in turn, accelerates the development and progression of the late complications of DM 2, worsening the prognosis of both DFS and CHF.

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The effect of chronic kidney disease on cardiovascular outcomes in patients with DM 2

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Aim
To study the role of chronic kidney disease (CKD) for cardiovascular outcomes in patients with DM 2
Material and methods
50 male patients (average age from 40 to 65 years) were identified at the time of diagnosis of DM2 with CRS from the databases of the department of diabetic nephropathy of the Center of Endocrinology named by Acad. Yo.Kh. Turakulov for the period 2022. Patients were under supervision after the diagnosis of adverse cardiovascular events – ACE- (myocardial infarction, stroke, AG, mortality), heart failure (HF) and CRC. Patients were distributed to 2 groups: 1 group – these are patients with DM2+ CKD (24 patients), 2 group – DM2+ CKD + HF + hypertension + hyperlipidemia (26 patients)
Results
CKD was associated with a higher risk of HF, mortality and ACE. This risk was more pronounced in elderly patients with the ACE in the history. ($P<0.05$). When analyzing in a general cohort in patients with DM2+ CKD + HF + hypertension + hyperlipidemia, the risk of the frequencies of the ACE was increased, HF compared to patients with DM2+ CKD. ($P<0.05$)
Conlusion
In patients with DM2, the presence of CKD was associated with a higher risk of ACE, HF and mortality.

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Mediastinitis complicating cervical cellulitis in a diabetic patient

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Introduction
Cervicofacial cellulitis represents one of the most worrying infectious emergencies in ENT despite their frequency which has clearly decreased since the advent of antibiotics. From a simple infection, most often dental or in the ENT sphere, it produces an infiltration of the cellulo-adipose tissue of the face and neck with extensive necrosis of the cervical and even mediastinal aponeurotic spaces especially in diabetic patients. The management must be rapid and efficient since the vital prognosis is engaged.

Aim
To study the clinical, radiological and the therapeutic modalities of mediastinitis complicating cervico-facial cellulitis in a diabetic patient.
Observation
This is a 62-year-old diabetic man, who consults ENT emergency for a left cervical mass associated with fever and asthenia since 2 days. Respiratory and hemodynamic status were preserved. The oral examination showed a defect oral hygiene with a decayed of the 41 tooth. The left cervical swelling was 10 cm, indurated and with inflammatory signs. The initial biological assessment shows a hyper leukocytosis at 327OO, a CRP at 319 mg/l and a blood sugar level at 12 mmol/l. Cervico-thoracic scan reveals a collection in the left anterolateral cervical spaces with wide pharyngeal communication, piriform sinus, extending to the thyroid cartilage taking off the thyroid gland, perioesophageal and reaching the anterior and posterior mediastinum. The dental panoramic shows a deterioration of the 41. An emergency flattening was performed after notifying cardiovascular surgeons for a possible thoracotomy. Bacteriological examination showed a very abundant and mixed bacterial flora reminiscent of anaerobic germs. Bi-antibiotic was initiated immediately. The dental treatment was carried out. Postoperative follow-up showed an improvement of the local condition and normalization of the inflammatory assessment.
Conclusion
Cervical cellulitis in diabetics is a serious condition requiring urgent and multidisciplinary care. The clinical presentation may sometimes underestimate the extent of the infection, causing life-threatening mediastinitis.

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Ramsay Hunt syndrome in a diabetic patient: A case report

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Introduction
Ramsay Hunt syndrome or Herpes Zoster Oticus is characterized by reactivation of latent varicella zoster virus in the geniculate ganglion and subsequent spread to cranial nerve. The diagnosis is mainly clinical. The facial paralysis seen in Ramsay Hunt syndrome is often more severe with the increased rate of late neural denervation and the decrease chance of complete recovery especially in diabetic patients. The aim of this study is to focus on the association between diabetes mellitus and Ramsay Hunt syndrome.
Case presentation
A 38-year-old woman with history of diabetes mellitus, on oral antidiabetic drugs and insulin, presented to ENT emergency with 4 days history of right-sided earache followed by the development of vesicular rash involving the right pinna. Physical examination revealed right-sided grade IV facial nerve palsy. The right ear had a cluster of vesicles on the concha and antihelix associated to perforated tympanic membrane in the otoscopy. Audiometry was normal. Random blood sugar was 18.3 mmol/l. We made a diagnosis of Ramsay Hunt syndrome and administered acyclovir 500 mg 4 times daily for 12 days and solumedrol 80 mg daily for 10 days. Two weeks after initiation of the treatment vesicular lesions disappeared but neurological examination revealed right-sided grade II facial nerve palsy. Blood sugar was well controlled.
Conclusion
Ramsay Hunt syndrome is one of the least frequent causes of facial palsy, inducing severe dysfunction and of poorer prognosis for the facial nerve than Bell's palsy. Associated acyclovir and high-dose corticosteroids with well controlled blood sugar improve facial nerve functional recovery in diabetic patients.

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Nasal septal abscess in patients with type 2 diabetes mellitus: A report of 2 cases

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Introduction
A nasal septal abscess (NSA) is defined as a collection of pus between the cartilage or bony septum and its mucoperichondrium or mucoperiostium. NSA caused by uncontrolled diabetes mellitus are rare. The aim of this study is to focus on the association between diabetes mellitus and NSA.
Materials and methods
We report two rare cases of NSA in patients with type 2 diabetes mellitus collected in ENT department of Farhat Hached Hospital of Sousse over a period of 10 years.
Results
Case one was a 80-year-old woman, with history of diabetes mellitus, hypothyroidism and on oral hypoglycemic medication, presented with a nasal block and purulent nasal discharge for 6 days. There was no history of trauma, sinusitis or any surgical procedures. Direct nasoendoscopy showed a bilateral septal swelling at the anterior aspect. Random blood sugar was 20.3 mmol/l. She had a surgical incision and drainage. The patient was started on IV cefotaxime and metronidazole than Clindamycin. She was started on sliding scale insulin for rapid blood sugar control. The microbiological examination showed *Staphylococcus aureus*. The follow-up was marked by the recurrence of the NSA leading to a revision surgery. No reccurence was noted. The second case was a 47-year-old man, with history of diabetes mellitus, on oral hypoglycemic medication, presented with an inflammatory nose swelling associated with bilateral nasal obstruction. He had no history of sinusitis, trauma or surgery. On examination, the patient had a fever at 39°c. The tip the nose showed localized edema and erythema with a healed carbuncles. Direct nasoendoscopy revealed bilateral septal swelling at the anterior aspect and bilateral inferior turbinate hypertrophy. Random blood sugar was 23 mmol/l. The treatment consisted on a surgical drainage and intravenous antibiotic therapy (cefotaxime and metronidazole). He was started on sliding scale insulin for rapid blood sugar control. Bacteriological examination showed *Staphylococcus aureus*. We noted the recurrence of the NSA within 7 days leading to a revision surgery. No reccurence was noted.
Conclusion
Nasal septal abscess is a rare condition. However uncontrolled diabetes should be considered as a condition in any patient with nasal septal abscess when trauma is excluded. Therefore prompt treatment should be given to prevent serious cosmetic nasal deformity and intracranial complications.

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Hypoglycemia in type 2 diabetes: Assessment of knowledge and fears

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Recurrent hypoglycemia is a major clinical problem. In fact, it disrupts blood glucose regulation and greatly impacts the daily lives of those affected. Maintaining glycemic balance is a real challenge indiabetic patients. The objectives of the study were to determine the prevalence of hypoglycemia in type 2 diabetics and to evaluate their knowledge.
Patients and methods
This was a cross-sectional study conducted among 120 type 2 diabetic patients followed at the outpatient clinic of the A service at the National Institute of Nutrition in Tunis. We evaluated the prevalence of hypoglycemia, their knowledge, clinical and biological characteristics of the patients, as well as methods of first line treatment of hypoglycemia and assessing fear of the risk of hypoglycemia using the HFS-II (Hypoglycemia Fear Survey-II) questionnaire.
Results
Our population consisted of 46 men and 74 women. The mean age was 58.4 ± .13.9. The average duration of diabetes was 12.1 years, the mean HbA1c was 9.85%. Only 25% of patients knew the definition of hypoglycemia and only 50% of them had a glucose meter. Among the studied patients, 43.3% had at least one episode of hypoglycemia in the month preceding the study. Adequate first line treatment in hypoglycemia was performed by only 16.6% of patients. Furthermore, the higher the HFS 2 Score, the more unbalanced the diabetes was ($P = 0.02$).
Conclusion
Preventing hypoglycemia is necessary in order to achieve good glycemic balance, hence the interest in therapeutic education that must be established early and regularly re-evaluated.

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Retropharyngeal abscess in diabetic patient: Management challenge

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Purpose
Retropharyngeal abscesses are rare in adults. They most commonly occur in immunocompromised patients as well as older one with systemic diseases like diabetes mellitus. The aim of this study is toidentify the clinical presentation of retropharyngeal abscesses and therapeutic challenges in diabetic patient.
Case report
It is about a 50-year-old man, diabetic (DNID) who consulted us for intense cervicalgia, odynophagia and mixed high dysphagia associated with fever. The patient received oral antibiotic treatment without any improvement. The physical examination found an apyretic and eupneic patient. Oropharynx examination noted halitosis and bulging of the anterior left wall. Neck examination revealed a tender left sided mass of 4 cm. Biological assessment revealed increased white blood cell counts and high sugar blood level. An urgent neck and chest CT scan showed a retropharyngeal circumferential fluid collection more pronounced on the left from the oropharynx down to the hyoid bone, with an important oedema of the vallecula and the epiglottis. Without extending into the mediastinum. The patient underwent early transoral drainage under general anaesthesia with intravenous antibiotic therapy (ceftriaxione + flagyl). Through the first week of hospitalization, blood sugar rates were out of balance. We noted the decrease of the cervical mass however the patient still complained about difficulty swallowing in solid food. A CT scan control at j10 of treatment revealed the increase of the retropharyngeal collection responsible for a significant mass effect on the aero digestive chain. That extend into the superior and posterior mediastinum. Revision surgery was required with transoral drainage and insertion of a tube feed. It was imperative to have the patient restrict oral intake until swelling resolves completely. Per operative bacteriological samples isolated klebsiella pneumonia resistant to cerftriaxone, thus we had to change the treatment by piperacillin–tazobactam. After one month of intravenous tazoactam therapy, we noted a visible clinical improvement and Cervical CT control showed total resolution of the retropharyngeal collection. The patient was discharged after 40 days of hospitalization. One month follow up, the outcome was favourable.
Conclusion
Retropharyngeal abscesses can quickly become a life-threatening emergency. Treatment consists of broad-spectrum antibiotics along with surgical drainage. Management in diabetic patient remains an interdisciplinary challenge including the expertise of specialists in otorhinolaryngology,endocrinologist, radiology, and microbiology.

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Multiple fingers with multiple endocrine disorders

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Background
Bardet–Biedl syndrome is a rare multisystem autosomal recessive disorder that falls under the spectrum of ciliopathy disorders. This ciliopathy is characterized by rod–cone dystrophy, renal malformations, polydactyly, learning difficulties, central obesity, and hypogonadism [1]. It was first described by Bardet [*2*] in 1920 and then by Biedl [*3*] in 1922. Its prevalence in Europe and North America is 1:100 000 [*4*]. The incidence of this syndrome is higher in the Faroe Islands and Kuwait, with 1:3700 and 1:17 000 live births, respectively [*5*]. According to the diagnostic criteria published by Beales *et al*., the diagnosis of BBS is based on the presence of at least four primary features or three primary features and at least two secondary features [*2*]. The management of BBS is supportive through a multidisciplinary team approach.
Case presentation
A 50-year-old single man presented to a university hospital, complaining of easy fatigue. The patient began to develop night blindness at the age of 7 years, and by the age of 15, he had entirely lost his vision. He had been diagnosed with diabetes mellitus for the preceding 6 years, and he had been managing it with insulin therapy and was experiencing frequent attacks of hypoglycemia. There is a history of polydactyly and visual impairment in the family. On physical examination, the patient was pale. He was 175 cm tall and 96 kg heavy, with a BMI of 31.3 kg/m^2, indicating obesity. His vital signs were normal. Fundus examination showed features of retinitis pigmentosa. Examination of the extremities showed post-axial polydactyly in both the upper and lower limbs. Laboratory investigations showed normochromic normocytic anemia, features of subclinical hypothyroidism, and a high renal profile. Abdominal ultrasonography revealed bilateral small kidney size, and echocardiography showed left ventricular hypertrophy. The diagnosis of BBS was made on the basis of the presence of four items of primary features (obesity, retinitis pigmentosa, post-axial polydactyly, and renal abnormalities) in addition to two secondary features (diabetes mellitus and left ventricular hypertrophy).
Conclusion
BBS is a rare clinical syndrome that may go unnoticed by many clinicians. Increased awareness among physicians is required for the early diagnosis and treatment of Bardet–Biedl syndrome and to avoid complications and mortality. The combined presence of post-axial polydactyly, blindness, learning disabilities, renal malformations, and obesity in a diabetic patient should alert to the possibility of BBS.

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EP553

Criteria for metabolic syndrome and assessment of biochemical indicators

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Metabolic syndrome (MS) is an actual problem of modern medicine. It is known that the prevalence of MS varies depending on the criteria used to determine it. It should be noted that the main criterion for MS is the central (abdominal) type of obesity. It is necessary to adapt the existing diagnostic criteria for MS in Russia, because it is necessary to take into account ethnic and genetic differences, national nutritional characteristics in the Russian population, lifestyle and economic opportunities. The purpose of the study: to evaluate the biochemical parameters and criteria for the metabolic syndrome.
Materials and methods
The study included 76 MS patients and 41 apparently healthy volunteers. The glucose level was determined by the glucose oxidant method, the lipid profile was assessed, and standard test systems were used. Insulin was determined by enzyme immunoassay using the DRG test system. All study participants signed an informed consent approved by the ethics committee. Statistical data processing was carried out using the application packages "Statistica for Windows 8.0".
Results
The results obtained show an increase in insulin resistance index (HOMA-IR) values with an increase in glucose or fasting insulin levels. This coefficient is of the greatest diagnostic value and has received wide practical application. The calculation of HOMA-IR revealed an almost 2-fold increase in this indicator in patients with MS ($P<0.05$), which is a predictor of the risk of developing vascular and diabetic complications. The level of NEFA in patients with MS was increased in 95% of cases and was almost 2 times higher than the norm. Also, in patients with MS, there was an increase in the level of insulin and glucose in the blood in comparison with the control group ($P<0.05$).
Conclusion
The study shows that early diagnosis of MS is important for providing timely medical care and lifestyle correction (weight loss, dietary changes, regular physical activity) and preventing the development of severe vascular and diabetic complications.

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EP554

Metabolic profile of morbid obesity compared with moderate and severe obesity: About 72 cases

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Introduction
Obesity is currently a public health problem due to its worrying increase in prevalence over the last ten years. The management of obesity and associated comorbidities is therefore a priority. The WHO classification distinguishes 4 types of obesity according to BMI in terms of severity.
Patients and methods
Retrospective study including 72 obese patients hospitalized and followed at the Endocrinology-Diabetology and Nutrition Department of the Mohamed VI

university hospital Oujda Morocco, divided into 2 groups, G1: 36 cases (BMI: 30 to 40 kg/m^2), G2: 28 cases (BMI $\geq$ 40 kg/m^2). Over a period of 2 years (from September 2020 to September 2022). Clinical and paraclinical data were collected from the patients' medical records. The analysis was performed by SPSS Version 21 software, and the threshold: $P<0.05$ was considered significant.
Results
In G1, the mean age of the patients was 33.19 $\pm$ 15.78 years and 39.61 $\pm$ 13.82 years in G2. A female predominance was noted in both groups, sex ratio F/H (G1): 3 and (G2): 8.33. The mean BMI in G1 was 35.56 $\pm$ 2.87 kg/m^2 and 47.01 $\pm$ 5.16 kg/m^2 in G2. The mean waist circumference was higher in G2: 131.98 $\pm$ 14.99 cm compared to G1: 113.71 $\pm$ 13.94 cm. The prevalence of diabetes was 27.77% (G1) and 28.57% (G2) ($P > 0.05$). The prevalence of hepatic steatosis was 52.94% (G1) and 48% (G2). The mean uricemia was 54.42 $\pm$ 14.59 mg/l (G1) and 65.47 $\pm$ 12.41 mg/l (G2). In contrast, the prevalence of dyslipidemia was significantly higher in the morbidly obese group (35.71%) compared to the moderate to severe obesity group (30.55%).
Conclusion
About Obesity is a complex chronic disease in which abnormal or excessive body fat (adiposity) impairs health, increases the risk of long-term medical complications and shortens life span. Our study demonstrates obesity increase metabolic risk whatever its severity.

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EP555

The association of cortisol secretion and body weight in overweight and obese patients

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Recently, 59 percent of European adults was diagnosed with obesity or overweight according to the 2022 Regional Obesity Report presented by the World Health Organization (WHO). Thus, insight into factors implicated in overweight and obesity may have important therapeutic implications. Interestingly, increased cortisol secretion and psychosocial stress have been demonstrated to be related with body weight-dependent insulin resistance and beta cells failure. Thus, the study was performed to assess the association of cortisol secretion, insulin resistance, and pancreatic beta cell failure occurrence. For the purpose of this study, 200 overweight and obese subjects (BMI $>$ 25 kg/m^2) and 50 healthy volunteers (BMI $<$ 25 kg/m^2) were enrolled. Study population was divided according to BMI values (into overweight (O1; BMI $>$ 25 kg/m^2) and obesity (O2; BM $>$ 30 kg/m^2)), homeostatic model assessment (HOMA) for insulin resistance (HOMA-IR) results (cut of 2). Simultaneously, among O1 and O2 study groups, the beta-cell function was assessed, and patients with pancreatic beta cell failure were appointed following HOMA estimates steady state beta cell function (HOMA-B) levels. The cortisol and adrenocorticotropic hormone (ACTH) concentrations were determined at Cobas E411 Roche device. The HOMA-IR and HOMA-B values were increased among O1 and O2 study groups comparing to control group ($P<0.05$, all). The cortisol concentration was increased in O2 comparing to control group ($P<0.001$). There were no differences in cortisol secretion in the O1 and control group. Nevertheless, comparing result obtained from patients among O1 and O2 groups with insulin resistance, the O1 patients were characterized with higher cortisol concentrations ($P<0.03$). Moreover, similar result was obtained among O1 and O2 patients characterized by pancreatic beta cell failure occurrence, where O1 patients were observed with increased cortisol secretion ($P<0.05$). The studied groups did not differ in ACTH concentrations. Based on the presented results, it can be assumed that obesity combined with insulin resistance or pancreatic beta cell insufficiency is associated with increased cortisol secretion.

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EP556

Child nutrition and the prevalence of obesity among the youth in Uzbekistan

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We examined the nutrition of 300 children aged 5–7 in households, preschool and school institutions and established that, surprisingly, that children's prescribed diet in the institutions includes a daily consumption of sweet tea, fruit compotes, cocoa and sweet carbonated drinks, and that the favorite food of children is sweet and fatty confectionery. An indispensable attribute of a typical school is a nearby retail outlets that profit from the desire of children to buy bright, cheap, but unhealthy low-quality sweets. Earlier studies of obese adults show that up to 35% of them suffered from obesity from early childhood. Considering that Uzbekistan is a country with a relatively young population (the average age in 2017 being 28.5 years), one can extrapolate a significant increase in obesity levels given these diets. In addition to school and household diets, the rollback of breastfeeding practices and the early introduction of complementary foods and cow milk contributes significantly to the predominance of childhood obesity. In Uzbekistan, the traditionally favored family model being many children (mostly one every two years), full breastfeeding of the newborn becomes a challenge, contributing to childhood obesity.

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EP557

Correlation of education levels with obesity and its treatment in Uzbekistan

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We studies the correlation between levels of educational attainment and the prevalence of obesity, as well as the effectiveness of its treatment surveying 200 patients of the Khorezm endocrinology dispensary in Urgench, Uzbekistan in March-October 2022. Lowest prevalence of obesity is, unsurprisingly, observed among the group with the highest educational attainment – in this group pre-obesity and 1st degree obesity prevail. Noteworthy, however, is a trend towards higher obesity among the educators and medics in that group, presumably due to the spread of IT technologies in Uzbekistani healthcare and educational facilities and its contribution to sedentary workplace. Professions typically associated with high levels of physical activity registered lowest levels of obesity prevalence – notably construction workers with only 0.09%. Among the professions cited obesity was most prevalent (78%) among drivers, with cooks (72%) and entertainers (67%) following them. Among state officials and public employees, a decrease in obesity prevalence could be registered, while the unemployed did not exhibit any significant trend. For the latter, given the predominance of housewives among the unemployed of Uzbekistan and given that they typically are not university graduates, one could extrapolate a trend towards obesity also in that group.

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EP558

Hirsutism and anthropometric parameters in obese Tunisian women: A correlation study

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Introduction
Hirsutism is a common disorder that occurs in 5% to 10% of women of reproductive age. The aim of this study is to evaluate the relation between anthropometric parameters (AP) and hirsutism in Tunisian obese woman.
Methods
A descriptive cross-sectional study was conducted at the obesity unit of the national institute of nutrition of Tunis including 65 obese women of reproductive age. data were collected by questioning, examining the patient and from medical records. The Ferriman-Gallwey score was used to evaluate hirsutism. Hirsutism was defined by a score higher than eight. Our population was divided into 2 groups: 26 hirsute women (H+) and 39 healthy women as a control group (H−). The AP considered were: weight, body mass index (BMI), waist circumference (WC) and body fat percentage (BFP). Testosteronemia was measured in hirsute women.
Results
The mean age of patients was 33.3 $\pm$ 10.8 years. Menstrual disorders were reported in 32.3% of cases. Morbid obesity was found in 34.9% of cases. Significantly higher differences between H+ and H− groups were shown regarding mean weight

(107.3 ± 25.5 versus 93.6 ± 14.7 kg; $P = 0.005$), mean BMI (40.5 ± 8.4 kg/m^2 versus 35.4 ± 5.5 kg/m^2; $P = 0.008$), WC (121.3 ± 17.1 cm versus 107.2 ± 11.7 cm; $P = 0.005$) and BFP (48.2 ± 7.1% versus 44.3 ± 4.6%; $P = 0.03$). A BMI above 36.9 kg/m^2 (OR = 5.4; $P = 0.004$), a WC above 109 cm (OR = 9.3; $P = 0.004$) and a BFP above 109 cm (OR = 6.9; $P = 0.005$) were significantly associated with the presence of hirsutism. In hirsute women, The mean blood testosterone level was 0.3 ± 0.2 ng/ml and there was a correlation between Testosteronemia and Weight ($P = 0.019$).

Conclusion

Our study clearly shows that hirsute women had higher AP. In fact, adipose tissue is implicated in the production of androgens. Therefore, weight loss of obese and overweight is strongly recommended.

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EP559

Eating disorders in an obese Tunisian population: Clinical and nutritional aspects

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Introduction

Eating disorders (ED) are very frequent in the obese population. Our objective was to describe the relationship between ED and the characteristics of an obese population (food intake, anthropometric measurements, cardiometabolic complications).

Methods

Cross-sectional descriptive study of 100 obese Tunisian patients followed at the obesity unit of the National Institute of Nutrition of Tunis.

Results

The mean age was 46.66 ± 12.32 years. The sex ratio M/F was 0.23. The average BMI was 40.3 ± 6.58 kg/m^2. Obesity class I, class II and morbid obesity were noted in 23.5%, 30.5% and 46% of cases, respectively. ED was noted in 84.3% of the cases and was dominated by snacking, compulsive eating, binge eating, night eating syndrome and bulimia in 53%, 52%, 48%, 36.3% and 22.5% respectively. We noted a significant association with the presence of at least one ED and the stage of obesity ($P = 0.036$). Patients with at least one ED had significantly higher energy, carbohydrate and simple carbohydrate intake than those without ED ($P = 0.011$, 0.001, 0.011 respectively) reflecting the poor dietary quality associated with ED. No significant association was found between APCs, anthropometric measurements and metabolic and cardiovascular complications apart from hypertriglyceridemia ($P = 0.012$).

Conclusion

The prevalence of APD is high in obese patients and is associated with poor dietary quality that leads to therapeutic failure. Our results are in agreement with those of DEDENON-MAYER(1).

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EP560

Complications of obesity in adolescents: About 18 cases

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Introduction

Adolescent obesity is a public health problem because of its prevalence and severity. It is a phenotypically heterogeneous disease and evolving in several phases (constitution, maintenance, aggravation) whose determinants are multiple. The great diversity of comorbidities and complications that can be experienced as a result of obesity makes all seriousness.

Patients and methods

Retrospective study including 18 obese adolescents hospitalized and followed at the Department of Endocrinology-Diabetology and Nutrition of the CHU Mohamed VI OUJDA, over a period of 2 years (from September 2020 to September 2022). Patients received an interview, a clinical examination and a biological assessment to rule out secondary obesity. Data were collected from medical records. The analysis was performed by SPSS Version 21 software, and the threshold: $P < 0.05$ was considered significant.

Results

The median age was 15.33 ± 3.30 years. The average BMI was 35.05 ± 6.61 kg/m^2. 6% of patients had overweight, 33% of patients had moderate obesity and 27% had severe obesity and 33% had morbid obesity. % of adolescents were in the dynamic phase of obesity. Complications were dominated by metabolic syndrome (29.41%), the average waist circumference was 110.29 ± 19.24 cm, 33.3% had hypoHDLemia, 22.2% had hypertriglyceridemia, 26.6% had prediabetes and 47.05% had hyperuricemia. Osteoarticular and pulmonary complications affected 17.6% and 17.6% of adolescents, respectively. Digestive complications such as fatty liver disease and GERD were noted in 5.8% and 11.1% of cases, respectively. None of the patients had Obstructive sleep apnea syndrome (OSAS) however 35.29% suffered from nocturnal snoring. The immediate consequences are often psychosocial.

Conclusion

These results justify the imperative of early and adequate management of obesity better than prevention, which must begin very early. Given the emergence of obesity among adolescents, preventive strategies are necessary, particularly targeting high-risk youth.

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EP561

The interplay between vitamin D deficiency and tuberculosis in patient with type 2 diabetes

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Introduction

The world medical community is strongly concentrated on the fight against infectious diseases, such as COVD-19, HIV/AIDS and tuberculosis (TB), but non-communicable diseases diabetes and complications "have relatively imperceptibly come to the fore in developing countries, becoming a global problem." The common multimorbidity disorders are evidence to suggest that, TB and vitamin D deficiency in patients with type 2 diabetes leads to disease clustering, frailty, and poor health-related quality of life.

Case report

A 62-year-old male has been suffering from type 2 diabetes for a long time complained of non-productive mild cough, low-grade fever, fatigue. A nasopharyngeal swab test for SARS-CoV-2 was negative. The patient consulted a tuberculotherapist. After the follow-up examination complete blood cell count, chest X-ray, sputum smear microscopy, genetic-molecular study with GeneXpert-test and culture test on the BACTEC system, the subject was diagnosed with disseminated TB with bacterial excretion, susceptible. The level of glycosylated hemoglobin (HbA1C) was 8.4%, glucose in the blood levels ranged from 3.2 to 15.4 mmol/l, 25-(OH)D_3 − 9.2 ng/ml, that severe vitamin D deficiency. The patient received treatment according to the 2HRZE 4HR scheme. At the patient's request, he continued to receive of antihyperglycemic drugs: metformin 2000 mg/day, sitagliptin 100 mg/day, but after one month therapy patient was given injection degludec/liraglutide at a daily dose of 10 units administered subcutaneously. The person is prescribed 20 000 IU/daily during 3 months. The result – the treatment was completed, whereas the cavern was preserved, the patient refused to undergo surgical treatment. After 3 months repeated laboratory tests were normal levels HbA1C was 7.1% without episodes of hypoglycemia and 25-(OH)D_3 − 20.2 ng/ml. The therapy resulted in patient's improvement of the general conditions and compensation of carbohydrate metabolism and vitamin D status.

Conclusion

Our clinical case suggests that the temporal relationship between significant deficiency vitamin D and the poor glycemic profile (HbA1C) in person with type 2 diabetes. TB programmes need to pay more attention to vitamin D status in the patients if there is coexisting diabetes. Particularly the association between vitamin D deficiency with prognosis of tuberculosis in patients with type 2 diabetes should be addressed through a future studies.

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EP562

Case of Severe (Familial) Hypertriglyceridemia with Metabolic Syndrome

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Introduction
Severe hypertriglyceridemia is a condition when triglycerides levels are over 500 mg/dl. It is serious risk-factor for cardiovascular disorders and acute pancreatitis. Especially in combination with glucose intolerance, abdominal obesity, and fatty liver.
Case
We present case of 27 y.o male with Severe Hypertriglyceridemia and Metabolic syndrome. 27 y.o male presented to clinic with several years of untreated Severe Hypertriglyceridemia history. He refused to take fenofibrate for years, but his triglycerides levels even on fenofibrate were never below 500 mg/dl.
Family history
Mom and Dad with Slightly elevated triglycerides and little brother with severely elevated triglycerides. Although Genetic testing was not done, we suppose that it is Familial Hypertriglyceridemia. He gained 20 kg past year. Height – 186 cm, Weight – 100 kg, BMI – 28.9 kg/m2. Waist circumference – 115 cm.
Laboratory Data: Triglycerides – >2625 mg/dl,
T-Cholesterol – 249 mmol/l,
HDL – 13 mg/dl,
LDL – 30.16 mmol/l,
VLDL – No results,
AI – 17.42.
HBA1c – 5.4%,
Glucose – 5.38 mmol/l,
Insulin Resistance index – 2.4,
Basal Insulin – 127.9 pmol/l.
TSH – in normal range.
Prescription
1. Lifestyle intervention (Healthy Eating Plan)
2. Fenofibrate – 145 mg daily
3. Rosuvastatin – 20 mg daily
4. Fish Oil – 4 g. daily
5. Metformin – 1000 mg daily
Follow-up after 2 months (January, 2023): 1. Weight loss – 10 kg. Height 186 cm, weight – 90 kg, BMI – 26.0 kg/m^2. Waist Circumference – 107 cm.
T-Cholesterol – 157.77 mg/dl
HDL – 27.456 mg/dl,
LDL – 69.6 mg/dl,
Triglycerides – 313.55 mg/dl,
VLDL – 62.64 mg/dl
AI – 4.75.
HBA1c – 5.4%,
Glucose – 4.95 mmol/l,
Insulin Resistance index – 2.19,
Basal Insulin – 119.6 pmol/l.
Patient continues healthy lifestyle modifications in his everyday living and Pharmacologic therapy without changes. Follow-up check-up in 3 months.
Conclusion
It is very important to increase awareness about hypertriglyceridemia and importance of dietary changes and pharmacological therapy especially in patients with familial hypertriglyceridemia and metabolic syndrome.

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EP563

Finerenone reduces Albuminuria in a non-diabetic female with congenital lipodystrophy

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Introduction
Chronic Kidney disease is one of the leading causes of morbidity and mortality worldwide especially among people with diabetes. Finerenone is non-steroidal emerging mineralocorticoid receptor Finerenone has proved to reduce albuminuria and delay the progression of CKD and reduce the cardiovascular risk in non-diabetic population. It is not known whether finerenone has the same effect in non-diabetic CKD. I used finerenone in a case of microalbuminuria in a female diagnosed with congenital lipodystrophy (images available) with normal HbA1c and preserved e GFR. Congenital Lipodystrophy is a group of genetic disorders characterized by severe insulin resistance and loss of adipose tissue with subsequent fat accumulation in the heart, kidneys, liver and ovaries. 22-year-old female presented with acromegalic facies lean body habitus and severe acanthosis nigricans. Her labs showed significantly elevated triglyceride more than 1000 mg/dl HbA1c 5.7%, Albumin-creatinine ratio was 50 mg/g, e-GFR was 120 ml/min, replacement of metreleptin isn't available in my country so I had to delay the progression of her albuminuria. She was given Finerenone 20 mg based on her serum potassium once daily for 3 months. After 3 months her albuminuria declined to 23 mg/g.

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EP564

New onset diabetes mellitus after dexamethasone treatment for intracranial hypertension in a case of severe acromegaly

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Introduction
Glucocorticoids are hormones that are used extensively in medicine for their anti-inflammatory and immunomodulatory effects. New onset diabetes mellitus is a frequent complication and is the result of an activation of glucocorticoid receptors which stimulate hepatic gluconeogenesis, adipose tissue lipolysis and increase the insulin resistance.
Case presentation
We present a case of a 49-year-old Ukrainian female who in 2015 started having headaches and a decrease in visual acuity. The dysmorphic features at the clinical exam were suggestive of acromegaly and an invasive 3 cm pituitary adenoma was found. The tumor was partially resected in 2015 in Ukraine, then the patient stopped seeing her endocrinologist until 2020, when an MRI showed an invasive 4 cm pituitary tumor. A somatostatin analogue treatment was introduced with poor medical adherence. The treatment was again interrupted in February 2022 due to drug shortage after the outbreak of Ukraine War. In April 2022 the patient was hospitalized in Romania and an IGF-1 of 837 ug/ml was detected. The MRI showed a minimal tumoral growth compared to 2020. A second neurosurgical intervention was refused because of major risks. A somatostatin analogue treatment was reintroduced along with growth hormone receptor antagonist and a dopamine agonist. Conventional radiotherapy was conducted during which the patient developed intracranial hypertension that required Dexamethasone. Blood sugar was monitored regularly during corticoid treatment and in July 2022 the patient developed diabetes mellitus (glycaemia 600 mg/dl, HbA1c 7.78%) that required basal bolus insulin regimen and Metformin. Dexamethasone was switched for Prednisone then it was gradually reduced and interrupted in august 2022. The insulin was interrupted in October 2022 and the Metformin treatment was continued because of a persistent impaired fasting glycaemia. The MRI at 3 months after radiotherapy shows a tumoral reduction compared to April 2022 (35/28/40 mm vs 35/30/47 in April 2022) and an IGF-1 value of 258 ng/ml, still slightly above the upper limit, so Pegvisomant was increased.
Conclusion
Glucocorticoids are very useful for their anti-inflammatory effect but they are associated with a wide range of side effects including disturbances of the carbohydrate metabolism, due to their stimulation of glucocorticoid receptors with a diabetogenic effect in different organs. New treatments that could retain the anti-inflammatory properties without having the diabetogenic effects are currently being researched. Selective glucocorticoid receptor agonists and 11beta-Hydroxysteroid dehydrogenase type 1 inhibitors are currently being tested in clinical trials but they show limited efficacy.

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EP565

A case report on hypertriglyceridemia induced pancreatitis

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Introduction
Acute pancreatitis is an inflammatory disease of the pancreas that can lead to necrosis of the pancreas and if infected could lead to multi-organ failure. Common cause of acute pancreatitis are gallstones and excess alcohol consumption. Hypertriglyceridemia is becoming an increasing cause of acute pancreatitis and is diagnosed with serum triglyceride levels >1.7 mmol/l. It is associated with high morbidity and mortality.
Case presentation
38-year-old male was admitted with left upper quadrant abdominal pain radiating to the back and vomiting. He was haemodynamically stable but was tachycardiac and

pyrexic. Past medical history of Diabetes Mellitus type2 on gliclazide and metformin, hypercholesteremia and hypertriglyceridemia on atorvastatin. However, he was not compliant with medication. He would on occasions consume alcohol in excess.
Investigations
Blood test showed raised inflammatory markers, WBC 15.2, CRP 220. Serum triglycerides were elevated 28.77 (normal limit < 2.26 mmol/l). Hyperglycaemia with blood glucose level of 17 and HbA1c 111. Amylase was raised at 378. The patient underwent CT Abdomen and Pelvis showing acute pancreatitis. No features of pancreatic necrosis or pseudocyst formation.
Management
Patient was initially managed conservatively with insulin sliding scale, intravenous fluids, analgesia and pabrinex. Started on Atorvastatin 80 mg and Fenofibrate 200 mg.
Discussion
Hypertriglyceridemia is a common form of dyslipidaemia that carries a high risk of cardiovascular disease such as atherosclerosis and hypertension. Hypertriglyceridemia results from environmental and genetic factors and is associated with other conditions such as obesity, diabetes mellitus, hypothyroidism and excess alcohol consumption. Chylomicrons are triglyceride-rich lipoprotein particles that are present when triglyceride are > 10 mmol/l and could occlude the pancreatic capillaries leading to ischaemia and enhanced lipolysis leading to release of free fatty acids, inflammatory mediators and free radicals that lead to inflammation, oedema or necrosis of pancreas. Hypertriglyceridemia induced acute pancreatitis associated with high morbidity and mortality risk and may lead to multi-organ failure. It is important to check lipid profile when a patient presents with acute pancreatitis. This can be managed with lifestyle changes and medications such as fenofibrate to help lower serum triglyceride levels below 4.5 mmol/l.
Conclusion
Hypertriglyceridemia is increasingly becoming a cause of acute pancreatitis which carries a high morbidity and mortality risk. It is important to consider this in patients presenting with acute pancreatitis and lipid profile should be requested as initial work-up. This could provide the opportunity to early diagnose hypertriglyceridemia and start treatment earlier to help prevent complications of pancreatitis and further episodes in the future.

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EP566

Major hypertriglyceridemia complicated by acute pancreatitis

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Introduction
Major hypertriglyceridemia is a rare pathology associated with severe acute complications. We report the case of a patient with major hypertriglyceridemia complicated by acute pancreatitis.
Observation
This is a 51-year-old patient with a history of hypertriglyceridemia on fenofibrate 160 mg per day and an attack of acute pancreatitis on chronic alcoholism. He consults for transfixing epigastric pain. The clinical examination found overweight (BMI at 29 kg/m^2) and android obesity. The biological assessment shows hyperleukocytosis with neutrophils, a CRP at 304 mg/l, a hypertriglyceridemia at 15.55 g/l, a hypercholesterolemia at 10.20 g/l, serum with a chylous appearance. Abdominal CT confirmed stage D acute pancreatitis. Treatment was started urgently with intensive rehydration, suspension of food, basal insulin therapy under cover with 5% serum glucose and heparin therapy at a preventive dose associated with analgesics. The patient also received treatment with fibrates and statins. The evolution is favorable clinically and biologically with a drop in triglycerides.
Discussion and conclusion
Major hypertriglyceridaemia is exceptional. Their severity is linked to the high risk of acute pancreatitis requiring early management.

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EP567

Why not MODY monogenic diabetes? A case report

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Introduction
Monogenic diabetes MODY is common but remains under diagnosed because genetic study is expensive in our country.
Method
We report the case of an 18-year-old patient with no personal pathological history admitted in October 2022 for diabetes management. Her diabetes was diagnosed accidentally on July 2022: Systematic capillary blood glucose done when she had a Hysteria's crisis revealed values higher than 2 g/l. From July to October, the patient did not received any antidiabetic treatment and never had any acute complication, especially ketoacidosis one. Our patient did not have cardinal signs of diabetes. The physical examination showed acanthosis nigricans and overweight (BMI = 25.7 kg/m^2). HbA1c was 9.9%, insulinemia and C-peptide were normal, and HOMA index was 2.52. Thyroid parameters and basal cortisolemia were normal. There were no pancreatic autoimmunity (negative anti-GAD 65, anti-islets and anti-insulin antibodies). The "MODY RISK" score was at 75%. The association of polycystic ovary syndrome or polycystic kidney disease was ruled out by radiological examinations. The patient was put on Glimepiride 1 mg/d and Metrormine 850 1 cp/d with achievement of glycemic targets. The genetic study was requested in progress.
Conclusion
Monogenic diabetes MODY has common characteristics with T1D and T2D. It is often underdiagnosed due to the cost of genetic study but it should be evoked when diabetes presentation is atypical.

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EP568

Type 2 diabetes and human immunodeficiency virus infection

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Introduction
Human immunodeficiency virus (HIV) infection and certain antiretroviral (ARV) treatments are associated with an increased risk of developing certain chronic comorbidities including type 2 diabetes, which is more prevalent in HIV-infected individuals. The coexistence of diabetes and HIV infection makes the standard of care more complex. The objective of this work is to discuss the relationship between these two comorbidities and to update physicians on the diagnosis of type 2 diabetes (T2DM) in HIV-infected patients.
Case presentation
A 40-year-old female patient, followed for HIV infection for 23 years under antiretroviral treatment, including protease inhibitors (PIs) and nucleoside analogues (NRTIs). Eight years later, the patient consulted with vaginal pruritus with profound asthenia. The workup showed fasting hyperglycemia at 3 g/l with hbA1c at 12%. She was put on insulin therapy and metformin with good evolution.
Discussion
It has been reported that diabetes is up to four-fold more common in HIV infected patients on retroviral therapy than in HIV seronegative patients. It is noted that glucose intolerance and insulin resistance are the main mechanism, the exact causes of which have not yet been defined, but several risk factors for the development of diabetes in HIV-infected individuals have been identified, such as duration of HIV infection, viral load, low CD4 count, and inflammation caused by HIV. However, the main factor that contributes to hyperglycemia in HIV is iatrogenic. Certain classes of AVR have been shown to increase the likelihood of developing diabetes in HIV-infected patients, such as protease inhibitors (PIs) and nucleoside analogues (NRTIs). And since HIV-infected patients have a more rapid turnover of red blood cells. It is suggested that fasting blood glucose should be used as a screening and diagnostic tool for diabetes in these patients, and postprandial blood glucose or oral glucose tolerance testing can also be performed as part of the screening measures.
Conclusion
As a result, the least toxic ARVs should be chosen and metabolic abnormalities should be detected early. Management should be multidisciplinary.

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EP569

Emotion sharing posts related to diabetes in Instagram

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Introduction
Diabetes is a disease affecting quality of life of millions of persons worldwide. Instagram is one of the most successful social media network. It influences, via its

posts, thoughts, emotions and decision making of many topics, including health related ones. The aim of this review to analyse the emotional sharing content of diabetes related posts in Instagram.
Methods
An Instagram query using the *search* term "diabetes" in arab language was performed between the 13th and th 23th January 2023. The first 10 posts appearing everyday of the study were included in the analysis. The publishing profiles, the nature and the content were assessed.
Results
70% of the overall diabetes related videos had emotional sharing content. Posts containing emotions sharing content had on average 932 likes and 132 commentaries; those with information sharing had 852 and 50, respectively. 32% of the videos shared positive emotions; it included mainly describing "success stories" of people living with diabetes, and "deculpabilisation" of diabetics. 7% contained negative emotions, mainly expressing difficulty of living with diabetes, and the insulin daily injection burden. 61% had neutral emotional content, mainly experiences sharing. 58% of positive emotions sharing was posted by diabetics profiles, and 15% by health professionnals.
Conclusion
The emotional sharing posts are popular among diabetes related content in Instagram. The posts published by diabetics had more positive percentage than other sharing profiles, and thus may be useful to help the diabetics improve their perception of their disease.

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EP570

Assessment of anthropometric parameters in type 2 diabetic patients on Liraglutide

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Introduction
Glycemic control and weight management are crucial considerations in the treatment of type 2 diabetes (T2D). Liraglutide, an incretin-based therapy, has been demonstrated to not only effectively maintain glycemic control but also promote weight loss in type 2 diabetic patients. Our study aims to evaluate the impact of Liraglutide on body weight and body composition parameters in patients with T2D.
Methods
This is a prospective study, carried out in the in the department of Endocrinology of the Military Hospital of Tunis. We administrated Liraglutide 1.2 mg daily at 22 patients with T2D. Weight and impedance measurements were performed on each patient before starting Liraglutide and after 6 to 12 months of treatment.
Results
Patients were 8 males and 14 females with a mean age of 53.8 ± 8.9 years. Our patients had dyslipidemia, hypertension, heart failure and coronary artery disease in respectively 16, 14, one and seven patients. Twenty patients were obese, with morbid obesity in 16 patients. The mean weight was 109.7 ± 17.9 kg before starting Liraglutide and 107.5 ± 18.6 kg after 6 to 12 months of treatment ($P = 10^{-3}$). The mean BMI was 40 ± 7.1 kg/m^2 before starting Liraglutide and 39.3 ± 7.4 kg/m^2 after 6 to 12 months of treatment ($P = 0.834$). The percentage of body fat decreased significantly after 6 to 12 months of treatment ($44.1 \pm 7.7\%$ vs $43.7 \pm 2.5\%$, $P = 0.046$). There was no significant change in lean body mass ($56.5 \pm 8.7\%$ vs $56.6 \pm 8.7\%$, $P = 0.930$).
Conclusion
Our study shows the effectiveness of Liraglutide in reducing weight and body fat percentage in patients with T2D.

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EP571

Reasons of Liraglutide discontinuation in Tunisian type 2 diabetic patients

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Introduction
Liraglutide is an anti-diabetic drug that has been shown to be effective for glycemic control and weight loss. However, factors such as unavailability, high cost, and side effects may make it challenging for patients to continue treatment. Our study aims to identify these barriers to treatment adherence and to understand the factors contributing to the discontinuation of Liraglutide therapy in Tunisian patients with type 2 diabetes (T2D).
Methods
A prospective descriptive study was conducted at the endocrinology department of the Military Hospital of Tunis, including 23 patients with T2D who were naïve to glucagon-like peptide-1 receptor agonists. Our study involved a progressive dosing regimen for Liraglutide, starting at 0.6 mg/day for one week, before increasing to the final dose of 1.2 mg/day. We have followed our patients for 12 months.
Results
Our population included 8 men and 15 women with a mean age 54.5 ± 9.5 years old. Mean duration of diabetes was 12.7 ± 8.2 years. Obesity, dislipidemia, and hypertension were found in respectively twenty, sixteen and 15 patients. Eight patients had a history of coronary artery disease. Four patients reported epigastralgia after the introduction of Liraglutide, associated with diarrhoea in one patient which persisted despite the reduction of the Liraglutide dose to 0.6 mg/day. Liraglutide treatment was discontinued in nine patients. The cause of withdrawal was digestive intolerance in two patients, lack of glycemic control with lack of weight loss in three patients, unavailability of treatment in three patients and death in one patient.
Conclusion
It is important to check the availability and tolerance of Liraglutide in diabetic patients, as this can help to better manage their diabetes and ensure that they are taking the most appropriate treatment.

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EP572

Therapeutic developments in diabetes mellitus

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Introduction
Diabetes mellitus (DM) treatment has recently undergone major developments which have dramatically changed the management of the disease. During the twentieth century major changes in the treatment of DM have transformed the disease from an uncurable disease to a chronic one. However, some of the major drugs used for its treatment have remained stable, while others have now almost gone into disuse.
Aim
The aim was to show the recent therapeutic developments in DM as depicted in everyday clinical praxis during the period 2016–2021.
Methods
The data of sales of antidiabetic medications in two medium sized pharmacies in central Athens during the years 2016 and 2021 were recorded.
Results
An increase in the sales of metformin by 22.2% was observed either alone or in combination with other orally administered antidiabetic medications. A major decrease in the sales of pioglitazone alone and in combination with other medications was observed. A major decrease in the sales of sulfonylureas was observed and glinides almost disappeared from the market. The sales of DPP-4 inhibitors either alone or in combination with metformin remained stable. A major increase in the sales of GLP-1 receptor agonists and of a combination of a GLP-1 receptor agonist and a long-acting insulin analog was found. A major increase in the sales of SGLT2 inhibitors was observed. The sales of human biosynthetic insulins decreased while the sales of long-acting insulin analogs increased.
Conclusions
In this report therapeutic developments in DM as depicted in the sales of antidiabetic medications in two pharmacies in central Athens are shown. Metformin continues to play a lead role in first-line treatment of DM 2. The sales of metformin increased and in 2021 they were 50% of orally administered antidiabetic medications and 40% of the total sales of antidiabetic medications. The sales of DPP-4 inhibitors alone or in combination with metformin remained stable, while GLP-1 receptor agonists and SGLT2 inhibitors increased dramatically. In this paper the major therapeutic developments in DM as they are depicted in clinical application in the urban multinational environment of central Athens, which may lead to the final cure of the disease are shown.

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EP573

The lipid spectrum of patients with diabetes mellitus 2 type and morbid obesity

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Aim of the study
To study the lipid profile of patients with diabetes mellitus 2 type (DM 2) and morbid obesity before bariatric surgery.
Material and methods
We evaluated 35 patients (15 women, 20 men) with DM 2 type and morbid obesity during October-December 2021. Mean age of patients was 48.3 years-old. Control group constituted by 20 healthy patients with same age. The patients were divided by BMI into 2 groups:
Group 1 – 17 patients with grade II obesity
Group 2 – 18 patients with grade III obesity
All patients underwent clinical and biochemical evaluations including endocrine check, lipids profile, hormonal profile (TSH, LH, FSH, prolactin, free testosterone, estradiol, progesterone, prolactin, etc), genitalia's ultrasonography, height (sm), weight (kg), BMI, waist circumference (WC), hip circumference (HC), waist–hip ratio, questioning and other studies.
Results
The study of anthropometry indicators revealed that 3 degree of obesity in all groups dominated:: in 1 gr - 64% of patients, 2 gr – 68%. The biochemical profile studies revealed violations of lipid metabolism – 84.6%: hypercholesterolemia –73.1%, reduced level of high density lipoproteins (HDL) – 73.1%, increased maintenance of low density lipoproteins (LDL) – 55.8%, hyperitriglyceridemia – 34.6%. A carbohydrate exchange disorders were found in all groups – insulin resistance – 88.5% of the total number of patients, hyperinsulinemia – 76.9%, violation of glucose tolerance – 46.2%.
Conclusions
1. In patients with Morbid obesity, 3 degree of obesity dominated in all surveillance groups. 2. The biochemical profile studies revealed violations of lipid metabolism – 84.6%: hypercholesterolemia – 73.1%, reduced level of HDL – 73.1%, increased maintenance of LDL – 55.8%, hyperitriglyceridemia – 34.6%

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EP574

The evaluation of anthropometric indicators after bariatric surgery in patients with DM type 2 and morbid obesity

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Aim
To study the dynamics of anthropometric indicators 3 months after bariatric surgery in patients with DM type 2.
Material and methods
We evaluated 35 patients (15 women, 20 men) with DM 2 type and morbid obesity during October–December 2021. Mean age of patients was 48.3 years-old. Control group constituted by 20 healthy patients with same age. The patients were divided by BMI into 2 groups:
Group 1 – 17 patients with grade III obesity.
Group 2 – 18 patients with grade IV obesity.
All patients underwent clinical and biochemical evaluations including endocrine check, lipids profile, hormonal profile (TSH, LH, FSH, prolactin, free testosterone, estradiol, progesterone, prolactin, etc), genitalia's ultrasonography, height (sm), weight (kg), BMI, waist circumference (WC), hip circumference (HC), waist–hip ratio, questioning and other studies.
Results
In 1 and 2 groups of patients we found a reliable decrease in BMI III and IV degrees 3 months after bariatric surgery.. In 1 and 2 groups of patients, a reliable improvement in indicators were noted compared to the average data of BMI.
Conclusions
Three months after the bariatric surgery in patients with DM 2 type, there is a reliable improvement in anthropometry indicators compared to the data before surgery.

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EP575

Lipemia interferences in clinical biochemistry parameters: a case report

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Introduction
Lipemic specimens could be a source of significant analytical errors. The aim of this study was to examine the effect of lipid removal using ultra-centrifugation of lipemic samples, on some routine biochemistry parameters.
Observation
A 53-year-old man hospitalized in endocrinology department for treatment of severe hypertriglyceridemia (21.3 mmol/l). All the patient's routine biochemical parameters were held on AU 680® Beckman Coulter before and after ultracentrifugation of the plasma sample. We determined total bilirubin, glucose, gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (PAL), amylase, lipase, creatine kinase (CK), lactate dehydrogenase (LDH), iron, cholesterol, triglycerides, HDL cholesterol, phosphorus, creatinine, urea, total protein, albumin, uric acid and magnesium. The percentage of differences (bias) was calculated and compared with the allowable inaccuracy. Clinically significant interferences were found in AST (14.81%), Total bilirubin (23.08%), lipase (27.06%), Total protein (1.47%) and magnesium (12.5%).
Conclusion
Lipemia causes clinically significant interferences for AST, Total bilirubin, lipase, Total protein and magnesium measurement on AU 680® Beckman Coulter and those interferences could be effectively removed by ultracentrifugation.

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EP576

The state of central hemodynamics in patients with diabetic foot syndrome is associated with chronic heart failure

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Aim
Study results of ultrasound dopplerography of the heart in patients with neuroischemic form of diabetic foot syndrome associated with chronic heart failure.
Material and methods
We examined 64 patients with DM 2 and DFS in the neuroischemic form on the basis of the Department of Surgery of the AndesMI. The patients were divided into 4 groups:1 gr – patients with neuroischemic form of DFS and CHF– 15 patients,gr. 2 – patients with neuroischemic form of DFS without CHF – 18 patients,Gr. 3 – patients with neuroischemic form of DFS, CHF and dyscirculatory encephalopathy stage 2–3 – 16 patients, gr. 4 – persons with CHF without D 2 15 patients. All patients were subjected togeneral clinical, biochemical, hormonal (IRI, C-peptide, inflammation marker-pro-inflammatory cytokine TNF-a, vascular endothelial growth factor (VEGF-A),and instrumental research methods – Doppler ultrasound of the vessels of the brain, lower extremities, ECG, Echo-ECG, bacteriological analysis of discharge from the wound, as well as statistical methods.
Results
There is a significant difference in the indicators of central hemodynamics in the studied groups compared with the norm: for example, LV EDR, ESV, EDV, LV EFR ($P < 0.05$), data on the average pressure in the pulmonary artery, the time of slowing the blood flow of early diastolic filling, TZSLV ($P < 0.001$);Thus, in patients of the studied groups, significant deviations of the Echo-ECG, which requires further study.
Conlusion
1. Among the risk factors, hereditary burden for DM dominated – only 21 cases out of 60 (35%), smoking – only 49 cases (81.6%), alcoholism

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EP577

The results of the early postoperative period in patients with DM 2 subjected to aorto-coronary bypass

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Aim
To study complications in the early postoperative period in patients with DM 2 subjected to ACB

Material and methods
60 patients (prospectively) with CHF were examinedafter endovascular revascularizationin the period of 2021 at the Center of Surgery named after acad. V.V. Vakhidov. All observed patients were divided into 2 groups: 1 gr. – 35 patients with DM2 with CHF and undergoing ACB, 2 gr. – 25 patients with CHF without DM2 who underwent ACBThe control group consisted of 20 patients with type 2 diabetes without CHF. To characterize the examined patients were used: general clinical, biochemical and instrumental examinations.
Research methods
General clinical, biochemical (bilirubin, direct, indirect, lipid spectrum, ALT, AST, coagulogram, blood sugar, glycated hemoglobin, urea, creatinine, GFR, galectin-3, insulin, renin, aldosterone in the blood) and instrumental: ECG, Echo-ECG, cardiac angiography, Dopplerography of the main vessels of the heart and legs, ultrasound of internal organs, fundus.
Results
We studied the systemic risk factors of atherosclerosis, such as age, gender, diabetes, hypertension and dyslipidemia, are to varying degrees of rejection of the graft. In the early postoperative period, these characteristics remained normal. In the early proverbial period, after A?B, our observation of complications was not observed.
Conlusion
Technical factors, such as the method used to harvest the conduits, the vasodilatory protocol, the storage solution, and the anastomotic technique, also play a major role in determining graft success.

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EP578

The role of risk factors in patients with Diabetes mellitus 2 and chronic kidney disease before hemodialysis

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Aim
To study the role of risk factors in patients with DM 2 and chronic kidney disease I–IV degree
Material and methods
The study was carried out in 30 patients with type 2 diabetes mellitus (DM 2) treated in the Diabetic Nephropathy Department 2019 – 2021. Healthy volunteers ($n=20$) amounted to a control group. The paper included general-clinical, clinical and biochemical, hormonal, immunological methods of blood testing, as well as instrumental methods of I investigation -ultrasound of internal organs, ECG, ECHO-ECG, indicators of the quality of life of patients (questionnaire), as well as statistical techniques.
Results
We analyzed 30 patients with DM 2, complicated by chronic kidney disease CKD 1–4 degree.. Of these, women – 12, men – 18. The average age of patients amounted to 56.3 / 67.5 years, respectively, among men and women. The following accompanying diseases were identified as the progression factors of the CKD: hypertonic disease – 74%, ischemic heart disease – 68%, chronic hepato cholecisto-pancreatitis – 62.7%, anemia – 45%, urine-stone disease – 25%, obesity – 17%, diseases of the spine –18.7%, transferred stroke – 9%, ovarian polycystic syndrome – 5%, etc.
Conlusion
Among the risk factors of CKD 1–4 degree. In patients with DM 2 first place was hypertonic disease and ischemic heart disease.

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Endocrine-related Cancer

EP579

Mathematical model for preoperative differential diagnosis for the parathyroid neoplasms

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Backgrounds
Preoperative diagnosis of parathyroid carcinoma (PC) is critical for the determination of the scope of surgical intervention. Nowadays, specific diagnostic markers for differentiation of PC and benign tumors are unknown, and less than half of patients with PC undergo necessary en bloc surgery.
Aims
To develop the instrument for preoperative diagnosis of PC.
Materials and methods
A multi-center retrospective study included 242 patients with primary hyperparathyroidism: 50 patients with PC, 30 with ?typical adenoma (AA), and 162 with adenoma of the parathyroid glands. We compared laboratory, instrumental and clinical characteristics. Comparison of two independent groups for quantitative data was performed using the Mann–Whitney test (U-test). Comparison of three independent groups for quantitative data was conducted using the Kruskal–Wallis ANOVA. The frequencies of binary variables were compared using the two-tailed Fisher exact test and Freeman–Halton test. The critical level of statistical significance for statistical hypotheses testing was taken as 0.05. CatBoosting algorithm was conducted to construct mathematical models for the differential diagnosis of PTG neoplasm types. Twelve factors were chosen by expert method for the model construction. At the first step, we reduced the dimension of feature space using sklearn.feature_selection, module ExtraTreesClassifier and SelectFromModel. Then we constructed the first model to differ PA and (PC or AA). At the second step, we also reduced feature space and constructed the second model to differentiate PC and AA.
Results
Patients with PC and AA had higher levels of PTH, ionized and albumin-corrected calcium, alkaline phosphatase, volume and the largest diameter of neoplasm, and the higher frequency of glomerular filtration rate decrease less than 60 ml/min per 1.73 m^2 compared to patients with adenoma. The frequency of low-energy fractures was higher in the carcinoma group versus the adenoma group (32% vs 8%). Heterogeneous structure and indefinite contour of glands detected by ultrasound were more typical for PC than for AA and adenomas. The mathematical model was developed using CatBoost gradient boosting algorithm for the noninvasive preoperative differential diagnosis of PC, AA, and adenoma.
Conclusions
Model can predict adenoma with PPV 100% and PC with PPV 81–92%. Using model clinicians could plan extended en bloc resection for PC and selective parathyroidectomy for adenoma. If AA is predicted, he has to make a decision on the choice of the necessary volume of parathyroidectomy based on his experience, because AA are the zone of uncertainty.

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EP580

Real world efficacy and safety of multikinase inhibitors in patients with advance differentiated thyroid cancer

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Purpose
To establish the safety and efficacy of multikinase inhibitors (MKIs) treatment in real life.
Methods
This retrospective observational descriptive study included patients with advanced differentiated thyroid cancer in treatment with MKIs as first and second line treatment. From November 2011 to May 2022. Clinical variables, efficacy and adverse events (AE) were collected. Variables are expressed as median and interquartile range.
Results
First line. $n=30$. 21 sorafenib, 6 lenvatinib, 2 axitinib, 1 pazopanib. Second line, $n=11$ lenvatinib. 46.7% were women. Papillary thyroid cancer 73.3%. Age of onset of MKIs 67 years. Time from metastasis to IMK start 24 (9.2–74) months. Lung metastasis 66.7%, bone metastasis 3.3%, lung and bone metastasis 20%.
Safety
AEs occurred in 96.7% of patients in first line treatment. The most common was asthenia in 70% of patients. Severe AE, grade 3 or 4, occurred in 30% of patients, the most common was palmar-plantar erythrodysesthesia syndrome. All patients in second line of treatment presented AEs. Asthenia was the most common AE (72.7%) followed by hypertension (63.6%). Severe AE occurred in 54.5% of patients.
Efficacy
MKIs as first line. The median progression-free survival (PFS) was 23 months (CI 95% 11.2–34.8). Median overall survival (OS) was not reached. Mean overall survival was 71.13 months (CI 52–90.1). Median duration of treatment 331 days. Sorafenib as first line. Median PFS was 16 months (CI 95% 4.8–27.2). Median overall survival (OS) was not reached. Mean overall survival was 64.3 months (CI 42.5–86.2). 3 patients died. Dose withdrawal because of AE occurred in 10

(47.6%) of patients. The rest had disease progression. Lenvatinib as first line. Median PFS was not reached. 1 patient died and 5 patients had not disease progression. Median duration of treatment 383 days. Lenvatinib as second line. Median PFS was 24 months (CI 16.6–31.4). Median overall survival (OS) was not reached. Mean overall survival was 36.3 months (CI 30.9–42.2). 2 patients died. Dose withdrawal because of AE occurred in 5 (45.5%) of patients who had disease progression. 2 patients suffered disease progression. Partial response occurred in 1 patient, 1 had stable disease.
Conclusions
With Lenvatinib as first line treatment, most patients reached stable disease. With sorafenib as first line treatment we got similar results to clinical trials. AE were common, 30% as first line and 54.5% as second line.

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EP581

A rare association of glucagonoma and gastric gastrinoma

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Introduction
Glucagonomas are rare functioning pancreatic neuroendocrine tumours that secrete glucagon. Gastrinomas are neuroendocrine tumours that secrete gastrin and are rarely located in the stomach. We report an extremely rare case of concomitant gastric gastrinoma and glucagonoma.
Case presentation
A 64-year-old-man with a history of digestive haemorrhage and gastrectomy presented with weight loss, asthenia, anorexia and abdominal pain. Esophagogastroduodenoscopy revealed severe erosive gastritis on gastrectomy stump, biopsy confirmed a grade 1 neuroendocrine neoplasm. Computed Tomography (CT) scan showed a 70-mm solid mass of the lesser curvature of the gastric stump, multiple liver metastases, multiple coelio-mesenteric adenopathies and partial thrombosis of the spleno-mesenteric trunk. A positive octreoscan was diagnostic for neuroendocrine tumour. Serum gastrin level was 108 pmol/l (normal $<$ 60 pmol/l). Once the diagnosis of metastatic gastric gastrinoma was made, the patient was put on somatostatin analogues. At one-year follow up, the patient reported itching cutaneous eruptions in his groin area treated with topical steroids with no improvement. These skin lesions were associated with weight loss, anorexia, glossitis and newly discovered diabetes mellitus. On physical examination, the lesions were suggestive of necrolytic migratory erythema. Laboratory tests indicated elevated blood glucose (12 mmol/l) and anemia (11 g/dl). Fasting glucagon level was elevated ($>$ 150 pmol/l, normal $<$60). Abdominal MRI showed a 10 mm peripheral nodule in the body of the pancreas.
Conclusion
The most interesting aspect of this case is the diagnosis of glucagonoma in a patient diagnosed with metastatic gastrinoma already treated with somatostatin analogues.

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EP582

Clinical characteristics and survival of patients with functional lung neuroendocrine tumors

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Aim
Functional neuroendocrine tumors (NETs) represent a specific diagnostic and therapeutic challenge. Hormonal clinical syndrome can severely complicate clinical picture and affect treatment. Functional pancreatic NETs have been extensively studied. Our aim was to analyze functional lung NETs in terms of clinical characteristics and survival.
Materials and methods
We retrospectively analyzed data from 230 patients with lung NETs treated at our department from 2005 till 2022. The patients underwent standard radiological, pathohistological and hormonal evaluation. All tumors were graded according to current guidelines to typical carcinoids (TC), atypical carcinoids (AC), large cell neuroendocrine carcinomas (LCNEC) and small cell lung carcinomas (SCLC). Disease stage was defined according to the ENETS/AJCC TNM staging system. Differences between functional and non-functional tumors were analyzed by non-parametric tests, overall survival was analyzed by Kaplan–Meier method, and differences by Cox-regression analysis. Statistical analysis was performed by SPSS software.
Results
Functional tumors were diagnosed in 53 patients (23%): 20 serotoninomas (8.7%), 15 with ectopic Cushing's syndrome (6.5%), 11 calcitonin secreting (4.8%), 6 with SIADH (2.8%), and 2 with ectopic acromegaly (0.9%). Sex distribution was almost equal in the entire group (female 50.4%), and in the subgroup of functional tumors (female 45.3% female). The mean age was 55.3 ± 13.6, with no significant difference between groups ($P=0.443$). Majority of functional NETs were well differentiated (TC 18.4%, AC 49.0%, LCNEC 22.4%, SCLC 10.2%), and this distribution was similar to patients with nonfunctional NETs ($P=0.127$). There were no significant differences in primary tumor size ($P=0.705$), and presence of MEN1 syndrome, but metastatic disease was less frequent in functional tumors ($P=0.01$), and consequently functional tumors more frequently presented in lower disease stages ($P=0.02$). Median overall survival in the entire group was 66.0 months (95%CI 35.7–96.3), and in the group of functional NETs 36.0 months (95%CI 4.7–67.3). Survival was significantly shorter in functional NETs compared to nonfunctional ($P=0.02$). When groups of different tumor grades were analyzed separately, significantly shorter survival of functional NETs was confirmed in well-differentiated tumors ($P=0.011$ for TC, and $P=0.009$ for AC), while poorly-differentiated tumors of both groups had similar survival ($P=0.585$ for LCNEC, and $P=0.632$ for SCLC).
Conclusion
Almost one quarter of patients with lung NETs have some form of recognizable hormonal syndrome. Even though functional lung NETs metastasized less frequently compared to non-functional, overall survival of these patients was significantly shorter, namely in groups of well-differentiated tumors. Treatment of these patients requires improvement of therapeutic strategies.

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EP583

Recurrent parathyroid cancer in a child associated with mutation in CDC73 gene

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Background
Parathyroid cancer (P?) in children is extremely rare, more often sporadic, but may be associated with a germline mutation. The only effective treatment is surgical approach due to the chemo-radio-resistance of PC.
Clinical case
A 6-years-old girl presented with weakness, gait disturbance, pain in the limbs, an X-shaped curvature of the legs. At the age of 12, the patient's well-being worsened sharply. The laboratory examination revealed primary hyperparathyroidism (PHPT): PTH 208 pmol/l, phosphorus 0.8 mmol/l, calcium ionized 1.76 mmol/l, alkaline phosphatase 4779 U/l. Ultrasound (US) showed a nodule $29 \times 17 \times 17$ mm near to the left lobe of the thyroid gland. At the age of 13, she underwent a selective parathyroidectomy with the achievement of remission. The histological structure was more consistent with a parathyroid adenoma (tumor structures in the lumen of some blood vessels were regarded as introduced during the preparation of the histological specimen). A germline heterozygous mutation c.70 G$>$T, p. Glu24Ter in exon 1 of the *CDC73* was identified. At the age of 15 years, there was a relapse of PHPT: PTH 527 pg/ml, Ca$++$1.4 mmol/l, total calcium 3.05 mmol/l. US visualized an hypoechoic lesion $8 \times 4 \times 6$ mm in the area of the removed PTG which accumulated ^{99m}Tc-MIBI on scintigraphy with SPECT-CT. The tumor of the left upper PTG with adjacent tissue was removed. Pathology examination showed invasive growth of PC into skeletal muscles and loss of parafibromin expression. One year later the patient underwent left hemithyroidectomy with ipsilateral lymphadenectomy, partial excision of the muscles, tissue and fascia to another recurrence of PC. Because of the PHPT persistence, a total thyroidectomy with pretracheal lymphadenectomy and the removal of lymph nodes, soft tissue on the right was subsequently completed followed by supraclavicular lymphadenectomy on the right. US and ^{99m}Tc-MIBI scintigraphy visualized an intramuscular neck lymph node (metastasis) $9 \times 12 \times$ 8 mm on the right accumulating the isotope. The ineffectiveness of the previous surgical treatment led to subsequent local radiotherapy (SOD 50 Gy) without remission achievement, however, in combination with cinacalcet 45 mg/day allowed to maintain mild hypercalcemia.

Conclusion
The bone deformities in childhood require calcium and PTH levels to be checked. If the diagnosis of PHPT is confirmed, a genetic study is necessary to exclude hereditary forms. A mutation in the *CDC73* gene should be aware of an increased risk of PC.

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EP584

Patient-derived three-dimensional model of papillary thyroid cancer for personalized medicine and testing of novel therapies

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Introduction
Over the last decades, there has been a significant increase in the incidence of thyroid cancer. Papillary thyroid cancer (PTC) is the most common histopathological type with often a favorable prognosis. Conventional therapies include surgical resection, adjuvant therapy with radioactive iodine, and suppressive therapy with thyroid hormones. However, the prognosis for iodine-resistant/refractory thyroid cancers or the advanced metastatic cancer is less favorable. We present the patient-derived three-dimensional (3D) model of PTC, which can be used to test novel therapies.
Results
3D cancer organ-like cultures (organoids) can be obtained from tumor resections or biopsies, propagated *in vitro*, frozen and thawed at any time. Organoid culture preserves genetic and cellular heterogeneity and allows determining individual responses of a tumor to drug therapies. To complement the existing protocols (Sondorp et al., 2020; Chen et al, 2021), we have developed an effective patient-derived 3D PTC models both for primary tumors and metastases. Pretreatment of cancerous tissue, culture medium, extracellular matrix and method of passaging are crucial for successful establishment of stable organoid cultures. Optimization of all the stages resulted in obtaining self-sustaining PTC organoid lines. Immunohistochemical analyses (anti-Ki-67, anti-TTF-1, anti-Thyroglobulin) and H&E staining of organoids and original tumor confirmed the malignant nature of the organoids, their heterogeneity and proved that PTC organoids recapitulate features (such as papillary, follicular or cystic structures) of the parental tumor tissue. The analyses were performed after at least three passages of the PTC organoid lines *in vitro*.
Conclusion
The presented model can be used for personalized medicine and development of optimal therapies for PTC.

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EP585

Phenotypic presentation of MEN1 (NM_130799.2):c.758delC (p.Ser253CysfsTer28) rs1592648765 pathogenic mutation of MEN-1 gene: a case report

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Multiple endocrine neoplasia (MEN) 1 is a rare hereditary autosomal dominant tumor syndrome characterized by two or more endocrine tumors. Non-endocrine neoplasms have been described as well. MEN1 is caused by inactivating mutations of the onco-suppressor gene MEN-1 (chromosome 11q13) which encodes the protein menin. Currently, 897 public variants of MEN-1 gene are reported. We present the case of a recently discovered pathogenic mutations of MEN-1 gene. A 32-year-old Italian male patient, admitted to our outpatient for osteopenia and nephrolithiasis in hypercalcemia and hypophosphatemia. Primary Hyperparathyroidism, confirmed both biochemically and morphologically (neck ultrasound plus ^{11}C-methionine PET-CT), was sustained by left superior parathyroid gland. The patient, after ruling-out pheochromocytoma diagnosis, underwent subtotal parathyroidectomy (left superior and inferior, right superior) since three hyperplastic parathyroid were found during the surgery. Pituitary hormones were evaluated, with no sign of pituitary hyper/hyposecretion, except for a single finding of high ACTH level. Pituitary MRI showed an 8 mm lesion suggestive for microadenoma. Cushing syndrome biochemical assessment was equivocal. The concomitant detection of high level of chromogranin A prompted us to perform an abdominal MRI, in the suspicion of neuroendocrine tumor (NET). The MRI showed three pancreatic lesions (12 mm in the pancreatic head, 8 and 3 mm in the pancreatic tail); moreover, it showed a 4 cm lesion of the medial lip of the left adrenal gland. ^{68}Ga PET-CT was performed, showing high radionuclide uptake, suggestive of high expression of somatostatin receptors, in the pancreatic area and left adrenal gland. Ultrasound endoscopy and subsequent biopsy of the pancreatic lesions confirmed the diagnosis of pancreatic NET G1. As regard the left adrenal nodule, no signs and symptoms of adrenal hormones hypersecretion were detected. The ^{131}I-Norcholesterol scintigraphy revealed a unilateral left adrenal gland uptake. The patient underwent left adrenal surgery due to the dimension of the nodule. Histology confirmed left adrenal adenoma. Genetic testing (MEN-1 gene exon 2-10 DNA-sequencing) identified a missense MEN1 heterozygous pathogenic variant MEN1(NM_130799.2):c.758delC (p.Ser253CysfsTer28) rs1592648765 in exon 4. The patient is now under somatostatin analogues and monitored by MRI and hormonal follow-up. Genetic inheritance is under investigation. We have described for the first time the clinical consequence of a recently discovered pathogenic mutation associated with four different endocrine neoplasms. MEN1 represents a complex syndrome, as it has plenty of possible clinical manifestations and a deep and still surprising panel of mutations and genetic variants. A potential genotype-phenotype correlation is still far to be recognized.

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EP586

Parathyroid carcinoma in a patient with both MEN1 and RET mutations

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Background
MEN1-related primary hyperparathyroidism (PHPT) characterised by benign course, whereas malignant transformation is extremely rare. The diagnosis of parathyroid carcinoma (PC) within the MEN-1 syndrome is a challenge for a range of specialists.
Clinical case
A 47-year Eastern European female. PHPT had been revealed during examination for multinodular goitre: PTH 614 nmol\l, calcium 3.06 mmol\l. Results of imaging methods were controversial (multiple lesions). The patient underwent total thyroidectomy and parathyroidectomy. Histological and immunohistochemical (IHC) examinations confirmed parathyroid carcinoma with the vascular and capsular invasion, spread to adjacent adipose tissue ??1N???Pn0LV, positive for PTH and Chromogranin A. The other parathyroid glands were described as adenomas. At the same time a neuroendocrine tumour of the lung (NET) 32×27×30 mm. (G2) was revealed. The patient refused surgery and further was treated with lanreotide 120 mg every 28 days. Hypercalcemia, hypercalciuria and low level of PTH were detected four years after primary surgery herewith she did not receive calcium and active vitamin D supplements. Bone scintigraphy excluded the osteoblastic process. 68Ga-DOTA-TATE PET/CT showed a lung tumour with increased growth up to 49×45 mm. IHC analysis of the bronchoscopic samples confirmed the highly differentiated lung NET expressing PTH. There was genetic screening at the age of 52 revealing mutations in the *MEN1* (1308G>A ?.W436X(NM_130799.2, pathogenic) and *RET* genes (HG38, chr10:43105062C>T, c.736C>T, with unknown clinical significance). The same MEN1-mutation was identified in her daughter, who was diagnosed with PHPT (parathyroid adenoma) and non-functioning pituitary microadenoma. Other components of syndrome manifested consistently. At the age of 50 she was diagnosed with pancreatic head tumour 31×34 mm, treated first with etoposide, carboplatin. Later pancreas body NET (19×13 mm., SUV=6.64), tail (11×9 mm., SUV =23.28 and 15×12 mm., SUV 15.22) were visualised on PET/CT. Pituitary macroadenoma 5.5×15×10 was identified at the age of 51. Due to an elevated level of IGF-1 and the absence of a decrease of tumour size, lanreotide dose had been increased to 120 mg every 21 days with the addition of cabergoline 0.5 mg once a week. The conservative treatment and follow-up are ongoing.
Conclusion
This case demonstrates the atypical genetic background in a patient with MEN-1 and PC. Despite the presence of *RET* mutation, components of MEN-2 syndrome

were not confirmed. The revealed hypercalcemia and hypercalciuria accompanied by suppressed iPTH allow us to assume the ectopic production of parathyroid hormone-related protein in the lung NETs.

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EP587

Prognostic impact of the tumor immune microenvironment in adrenocortical cancer

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Background
Adrenocortical carcinoma (ACC) is an uncommon endocrine malignancy, usually characterized by a late detection, aggressive clinical course, and poor outcome. The tumor microenvironment (TME) which includes infiltrating immune cells plays a critical role in tumor growth, survival, and prognosis in cancer patients. The presence of tumor-infiltrating immune cells (TIIC) affect the clinical benefit from novel strategies of immunological checkpoint blockade. Anti-immune pathways like PD-L1 are used by the tumor to overcome immune system and they serve as immunotherapy targets.
Methods
The study included tumor tissue samples from 75 patients with ACC, which treated at the Endocrinology Research Centre (Russia, Moscow) between 2010 and 2022: 47 cases of conventional (62.7%), 18 cases of oncocytic (24%), and 9 cases of myxoid (12%) and 1 case of sarcomatoid (1.3%) variants of ACC. Immunohistochemical analysis of tumor tissue sections was carried out according to the standard technique with a peroxidase detection system with DAB on an automatic Leica BOND III IHC staining system using Leica reagents and protocols. Each of the 75 patients underwent histological diagnostics and a series of immunohistochemical stains for the markers of the main immune cell subsets: CD45, CD3, CD4, CD8, and CD68. The impact of PD-L1 expression and the number of TIIC considering the intratumoral and stromal distribution on pathological characteristics and clinical outcomes were analysed.
Results
The number of ?D45+ immune cells in tumor parenchyma and stroma was 189 and 268 cells/mm^2, respectively. However, the number of immune cells from all the analyzed populations in tumor parenchyma was higher in oncocytic compared to conventional ACC cases. The analysis of the relationship of survival with the studied factors showed that the overall survival and progression-free survival between conventional and oncocytic histological variants differ significantly. The differences in survival between conventional and oncocytic histological variants of ACC were statistically significant (P-value < 0.05). PD-L1 expression does not affect prognosis.
Conclusions
Rich T-lymphocyte response is a good prognostic factor in ACC. The study of TIIL subpopulations can be used to predict ACC outcomes.

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EP588

An unusual association of a familial MEN1 with renin co secretion form a glucagonoma

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Introduction
Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder consisting in the development of primary hyperparathyroidism (PHPT), pancreatic neuroendocrine tumors, and pituitary adenomas. Occurrence of glucagonoma in MEN1 patients is rare (3%) and metastatic disease is present in 50% to 80% of patients at the time of diagnosis. The association of adrenal nodules/tumors and MEN1 is also rare.
Case report
We present the case of a 37-year-old female patient with a personal history of type II diabetes mellitus and severe hypokalemia who presented to the "C.I Parhon" National Institute of Endocrinology for further investigations of hypopotasemia. She had normal blood pressure, weakness and fatigue. Laboratory showed high values of renin and aldosterone (renin >300 pg/ml, aldosterone 547 pg/ml) with persistence of severe hypopotasemia (K = 2.30 mmol/l), hyperparathyroidism (PTH = 324.10 pg/ml with normocalcemia), hyperprolactinemia (PRL = 91.93 ng/ml), without hypercortizolism. Chromogranin A = 1.700.00 ng/ml and glucagon were high, with normal levels of 5HIAA, NSE and serotonin. Abdominal MRI reveals a pancreatic corporeal-caudal tumor mass whose appearance is compatible with a neuroendocrine tumour with secondary lymph node and liver determinations. Parathyroid scintigraphy identified an aspect suggestive of lower left parathyroid gland. It was decided surgery, with enucleoresection of cephalopancreatic exopthytic tumour, corporal-caudal splenopancreatectomy en bloc with partial left adrenalectomy. Pathology certifies a well-differentiated neuroendocrine tumor G1pT3pN1pM1a and immunohistochemistry shows positivity for AE1-AE3, chromogranin and synaptophysin, negative staining for CD56, Ki67 $<1\%$. Microwave ablation of tumoral liver segment VII was performed considering secondary determinations in the liver. Medical management included somatostatin analogues.
Conclusions
The discovery of elevated levels of renin in the presence of glucagonoma in this patient suggests a tumoral co-secretion. This association is very rare and constitutes a life threatening situation, requiring multidisciplinary approach.

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EP589

Alpelisib-induced severe hyperglycemia: A case report. Are we discontinuing the drug too soon?

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Background
Alpelisib is an α-selective PI3K inhibitor indicated for the treatment of postmenopausal women and men with hormone receptor-positive (HR+), human epidermal growth receptor 2-negative (HER2–), PIK3CA-mutated locally advanced or metastatic breast cancer following disease progression or after endocrine therapy. Hyperglycemia is the most common adverse event (up to 60%) associated with its use. It occurs more frequently and lasts longer in patients with prediabetes or type 2 diabetes (DM2) at baseline. 4 grades of Alpelisib-induced hyperglycemia are defined by the FDA. In grades 3 (>13.9–27.8 mmol/l) and 4 (>27.8 mmol/l), current guidelines recommend to interrupt or even discontinuate Alpelisib.
Case report
We present the case of a 58-year-old woman with a history of hypertension, dyslipidemia, obesity, and untreated type-2 diabetes. In 2010, she received surgery for breast cancer (HER2+, HR+, PIK3CA-mutated). Since 2018, lymph node and bone progression were discovered despite hormonal treatment and radiotherapy for symptomatic control. She started treatment with Alpelisib-Fulvestrant in July 2022, with grade 3–4 hyperglycemia (9–15 mmol/l) appearing after a week. She was referred to an Endocrinologist and began treatment with a low-carbohydrate diet, metformin titrated to a maximum dose of 1000 mg twice a day, linagliptin 5 mg once a day and insulin therapy in a basal-bolus regime at 0.2 IU/kg (Table 1). Despite this treatment, in the following months both fasting and postprandial blood glucose levels remained between 10 and 15 mmol/l, so it was necessary to increase the insulin dose progressively. In November 2022, high blood glucose levels persisted, with the control CT scan showing stable disease. She continued Alpelisib and kept increasing insulin dose up to 0.95 IU/kg. In January 2023, glycemic targets were achieved (preprandial 5–6.66 mmol/l, postprandial 5.55–9.99 mmol/l, HbA1c of 7.3%) and dose was even lowered up to 0.7 IU/kg to prevent fasting hypoglycemia.

Table 1 Hypoglycemic agents used in the case report. IU = international units.

	Aspart U100 (IU)					
	Breakfast	Lunch	Dinner	Glargine U300 (IU) at 2200 hours	TOTAL (IU/kg)	Other
07/2022	4	4	4	10	0.20	Metformin 1000 mg (1-0-1)
11/2022	16	16	16	38	0.95	Linagliptin 5 mg (0-1-0)
01/2023	11	10	16	30	0.70	Low carbohydrate diet

Conclusion
Grade 3–4 AIH management with low CH diet, metformin, linagliptin and basal-bolus insulin therapy at high doses has allowed our patient to accomplish hyperglycemia control after 6 months of treatment, without interrupting Alpelisib while achieving stable oncological disease to date.

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EP590

Incidental diagnosis of MEN2a in a patient with concurrent ovarian carcinoma presenting with cervical lymphadenopathies

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Introduction
Multiple endocrine neoplasia type 2A is an autosomal dominant disorder which is characterized by the occurrence of medullary thyroid carcinoma in association with pheochromocytoma and parathyroid tumors.
Case report
We present the case of a 64-year-old woman, with familial history of thyroid carcinoma, renal lithiasis and personal history of right nephrectomy for renal lithiasis, who presented for the investigation of a left lateral cervical mass. CT scan revealed bilateral thyroid nodules, multiple lateral cervical and supraclavicular lymph nodes metastasis, left ovarian tumor with lumbar, paraaortic and interaortocaval lymph nodes metastasis and small adrenal left nodule. Biochemistries revealed a high level of calcitonin 792 pg/ml, carcinoembryonic antigen 84 ng/ml, hypercalcemia 11 mg/dl, increased PTH 140 pg/ml, normal levels of plasma and urine metanephrines, normetanephrines. DNA testing of the RET proto-oncogene revealed the Cys634Arg mutation, confirming the MEN2 diagnostic. Bilateral ovariectomy, total hysterectomy and dissection of lomboaortic, interaortocaval lymph nodes were performed, testified by histopathological findings as high grade papillary serous ovarian carcinoma. Two months later, a total thyroidectomy, left superior parathyroidectomy and lateral neck dissection were performed. The histopathological examination confirmed bilateral medullary thyroid carcinoma, with 13 secondary metastatic lymphadenopathies due to ovarian carcinoma and parathyroid adenoma. Immediate postoperatively biochemistries were: calcitonin 41 pg/ml, PTH 10 pg/ml, normal total calcium, and at two months follow-up calcitonin 2.9 pg/ml, PTH 88.2 pg/ml, normal total serum calcium, carcinoembryonic antigen 2.23 ng/ml. Three years follow up CT scans showed no signs of relapse or secondary metastatic lesions.
Conclusions
When diagnosing a patient with MEN2A is important to look for clinical and biochemical features along with personal and family history and genetic testing. The incidental diagnosis of MEN2A allowed us to plan the genetic screening of the proband's family. We anticipate that the multidisciplinary approach for treatment and follow-up investigations will increase the survival prognosis of our patient.

Keywords: MEN2A, papillary serous ovarian carcinoma

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EP591

The correlation between baseline calcitonin levels and the risk of metastasis in patients followed for medullary thyroid carcinoma

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Introduction
Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor that represents the most aggressive form of thyroid carcinoma, usually diagnosed at advanced stages. Serum calcitonin (CT) is the sensitive and specific marker of sporadic and hereditary CMT. It is a diagnostic, prognostic and follow-up marker.
Purpose of the study
To investigate the correlation between the risk of metastasis and CT levels at the time of diagnosis of MTC.
Materials and methods
Retrospective study including patients followed for MTC in the endocrinology and diabetology department of the CHU Ibn ROCHD in Casablanca from 2007 to 2022. The statistical analysis was carried out by the SPSS 25.0 software.
Results
We recruited 25 patients followed for CMT; the average age was 46.9 years, with a female predominance (72%). All patients underwent total thyroidectomy, bilateral lymph node dissection was performed in sixteen patients and unilateral in three patients. The MTC was in the context of MEN in six patients (24%), the genetic study of mutations of the RET proto-oncogene was positive in three patients. Fifteen of the cases presented a metastatic form (60%), the lymph node localization of which was present in all patients and at a distance in ten patients (66.7%). The CT level at the time of diagnosis in patients with a metastatic form was $>$ 500 pg/ml (mean value 3855.6 pg/ml) in 66.6% of patients ($P<0.01$), while the CT level was $<$ 100 pg/ml in patients without metastases. Most had undergone a first incomplete thyroid surgery. Moreover, the tumors were larger, multifocal ($P<0.05$) and with capsular invasion ($P<0.02$). Among these patients, three benefited from chemotherapy sessions, radiotherapy was performed in two patients, one patient was put on targeted therapy with vandetanib and two patients are scheduled for treatment with sorafenib.
Conclusion
CT is a very sensitive biochemical marker. The absence of its preoperative assay leads to a delayed diagnosis of MTC and the initial surgery is often incomplete. Indeed, preoperative CT levels are strongly correlated with disease progression, which requires adequate management with close monitoring of the disease.

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EP592

Ferroptosis in human adrenocortical cells and aldosterone-producing adenomas

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Background
The role of ferroptosis – a regulated form of cell death – in the pathophysiology of aldosterone-producing adenomas (APA) is unclear.
Objective
To identify mechanisms of ferroptosis in human adrenal cells and translate these findings to APA pathophysiology.
Methods
Cell death detection, lipid ROS generation and mRNA sequencing were performed on HAC15 cells treated with the specific ferroptosis inducer RSL3 (1, 2 and 4 mM), in the presence and absence of the ferroptosis antagonist Liproxstatin-1. Volcano plots and heat maps were used to visualize RNAseq data from RSL3-treated HAC15 cells. Transcriptomics data of APAs versus adjacent cortex were mined from a publicly available transcriptome dataset (GSE60042). Spatial gene expression profiles of selected genes of interest were generated in 8 cryosections of APAs and paired adjacent cortex.
Results
RSL3 induced a liproxstatin-1 sensitive, dose-dependent effect on HAC15 cell death and lipid ROS generation. Genes which were differentially expressed in both RSL3-treated HAC15 and in APAs were identified and considered as genes of interest. RSL3 induced dose-dependent increases in *HMOX1*, *UNKL* and *TRIB1* gene expression in HAC15 cells. The spatial transcriptomics dataset showed decreased *HMOX1*, *UNKL* and *TRIB1* expression in APA tumor tissue relative to the adjacent cortex. Therefore, we identified genes with a putative function in the promotion of ferroptosis in human adrenal cells which were downregulated in APA tumors.
Conclusion
Suppression of cell death by ferroptosis may play a key role in APA pathophysiology.

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EP593

Endocrinopathies in oncological patients treated with immunotherapy: A real world data study

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Background
Immune checkpoint inhibitors (ICIs) (anti-CTLA-4, PD-1 inhibitors, PD-L1 inhibitors) are considered a widely used therapeutic choice for several cancer

types. However ICI therapy is frequently complicated by adverse events; endocrine toxicities are the most common ones.
Methods
To assess in a retrospective observational study in a tertiary hospital the incidence and the characteristics of the immunotherapy-related endocrine adverse events (irEAEs) in oncological patients treated with ICIs. All patients had baseline hormonal functional tests (before the initiation of ICIs) and during the follow-up (mean: 20 months).
Results
A total of 117 irEAEs cases were registrated out of 1077 (10.86%) oncological patients treated with ICIs (46% females). The mean time of diagnosis of irEAEs was 7.7 months after the onset of ICIs treatment with recovery in 9.4% of patients during the follow-up. The overall incidence of hypophysitis and thyroid dysfunctions was 6.9% and 4% respectively in patients treated with ICIs. Among the 117 irEAEs cases, 63.2% (74 cases) presented with hypophysitis followed by 24.8% with primary hypothyroidism (29 cases) and 10.3%with thyreotoxicosis (12 cases). Furthermore, one case developed diabetes insipidus, one case primary adrenal insufficiency and two cases primary hypogonadism. Hypophysytis was diagnosed in 75% of patients treated with anti-CTLA-4 inhibitors vs. 61.5% of patients treated with PD-1/PDL-1 and 72.4% with combination treatment. Thyroid disorders were noted in 36% of patients treated with PD-1/PDL-1 vs. 25% of patients with anti-CTLA-4 inhibitors and 25.5% with combination treatment. Hypophysitis was reversible in 9.5% of patients whereas primary thyroid disorders in 25.8% of cases with irEAEs. Interestingly reversibility was significantly associated with the time of diagnosis of irEAEs. Thyroid autoantibodies were found positive in 44% of cases with primary hypothyroidism and in 30% of cases with no thyroid dysfunction. No MRI was performed systematically among patients with hypophysitis. However in 20 out of 34 (58%) of patients with hypophysitis, MRI presented pathological findings.
Conclusions
irEAEs are relatively frequent in patients treated with ICIs, thus physicians should be aware of the clinical signs/symptoms in order to proceed to an early diagnosis and treatment. The complexity of the pathophysiological mechanisms of action of ICIs requires a multidisciplinary approach of these patients.

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EP594

Psychiatric disorders in Cushing's syndrome and impact on follow-up

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Introduction
Cushing syndrome (CS) is a rare and serious disease with high mortality. Diagnosis and management of the disease are difficult, as CS is typically characterized by the presence of multiple symptoms hypertension, diabetes, weight gain, or osteoporosis, the psychiatric and neurocognitive consequences are just as important by a set of anxio-depressive disorders resounding on the quality of life but also on the management of the disease.
Objective
Describe the association of Cushing's syndrome with anxiety and depression disorders and retention on adherence to treatment and follow-up of the disease.
Methods
Descriptive retrospective study of patients hospitalized for endogenous hypercortisimes in the endocrinology and metabolic diseases department between 2018 and 2022.
Results
Our study included 64 patients, the average age was 29.6 years, with a clear female predominance. memory loss with difficulty concentrating was noted in 95%, insomnia with difficulty falling asleep in 80%, depression in 75%, a psychiatric consultation was carried out in the majority of our patients, 50% were put under anxiolytic and antidepressant treatment, only one case of visual hallucination was recorded. As for adherence to treatment and follow-up, 82% showed up regularly for consultation, 6% intermittently and 12% were lost to follow-up.
Conclusion
Psychological management is part of the multidisciplinary management of Cushing's syndrome. Psychological interventions may be required to treat depression and to improve long-term prognosis, subjective wellbeing and quality of life.

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EP595

Immune checkpoint inhibitors induced endocrinopathies: a possible indicator of improved survival

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Background
Immune checkpoint inhibitors (ICI) are an innovative oncologic therapy used in several types of solid and hematological neoplasms. This treatment enables the antitumoral immune system response and results in significant improvement of clinical outcomes and survival rate. However, endocrine related adverse effects (ERAE) have been related, with thyroid and pituitary dysfunction being the most common endocrine diseases described. An association between the surge of endocrinopathies and better overall survival rate has been suggested.
Aim
To evaluate the association between patients' features and the development of endocrine toxicity and to assess the association between ERAE development and mortality.
Methods
A retrospective observational study was conducted in 98 patients submitted to immunotherapy in our center since its introduction in 2015 until March 2021. We excluded patients who had missing data regarding the corticotroph axis evaluation. We used linear and logistic regression models to address our aims.
Results
We observed a significant negative association between ERAE development and death (OR 0.32; $P=0.028$). We detected no associations between ERAE and the following characteristics: age at ICI initiation, sex, diabetes *mellitus*, medical history, immunotherapy duration and ICI type.
Conclusion
The development of an ERAE may be associated with a better overall survival rate in advanced oncologic disease supporting the role of an unleashed immune system response to malignant cells.

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EP596

Case Report: Successful treatment of an atypical lung neuroendocrine neoplasm with PRRT

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Neuroendocrine neoplasms (NENs) arise from specialized cells called neuroendocrine cells spread through the body, mainly in the gastrointestinal tract, pancreas and lung. Pathological classification of Lung NENs include well differentiated NENs, that can be classified as typical or atypical carcinoids, and poorly differentiated neuroendocrine carcinomas (NECs), classified as small-cell lung carcinoma (SC-NEC) or large-cell neuroendocrine carcinoma (LC-NEC). We present a case of a 59-year-old female patient, who was referred to our hospital in 2012, for treatment with Peptide Receptor Radionuclide Therapy (PRRT) with ^{177}Lu-DOTATATE, due to progressive metastatic NEN lung disease. The patient had previously been submitted to primary tumour ressection, in 1999, with histopathological diagnosis of an atypical lung carcinoid. Due to metastasis in liver (2008), bone (2009) and kidney (2012), the patient underwent various treatments, namely somatostatin analogues (2008); chemotherapy (may 2008-June 2009); anti-algic radiotherapy (2009) and sunitinib (July 2009-february 2012). She was referred to IPO Porto, due disease progression despite multiple treatments. As she had high expression of somatostatin receptors on ^{68}Ga-DOTA-NOC-PET/CT, the patient underwent 3 cycles of PRRT treatments from 2012 to 2013 (Before NETTER-1 results). A dose adjustment in the administered activity was made, due to higher treatment toxicity risk of the patient, given her clinical background of chronic kidney disease (GFR ~48 ml/min). Despite the reduced treatment activity (total: 14.99 GBq), treatment response was obtained (imaging improvement, with visualization of fewer foci of ^{68}Ga-DOTANOC PET/CT uptake at liver and bone level). No renal or hematological toxicity occurred. Disease progression was diagnosed in ^{68}Ga-DOTANOC PET/CT in may 2016, with new bone and hepatic lesion detected however not detectable by CT imaging. After 10 years, the patient remains clinically stable, under treatment with cold somatostatin analogues. Despite PRRT with ^{177}Lu-DOTATATE not being yet approved by the EMA for treatment of lung NETs, this case illustrates the potential clinical benefit of this treatment in this group of patients. Besides, chronic kidney disease (CKD) patients should have

individualized approach as they can benefict from PRRT at lower doses, with clinical and imagiological response. Randomized clinical studies are needed to validate PRRT in lung NENs.

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EP597

Diagnostic efficacy of tumor markers in the detection of metastatic pancreatic neuroendocrine neoplasms

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Introduction
Neuroendocrine neoplasms (NENs) are rare heterogenous tumors which prevalence is increasing. Functional pancreatic neuroendocrine neoplasms (p-NENs) develop characteristic clinical syndromes in contrast to non-functional tumors that are diagnosed accidentally or at an advanced stage due to the lack of sensitive and specific biomarkers that could predict their clinical course.
Aim
This study aimed to assess tumor markers (TMs) in patients with p-NENs and their association with disease extent (metastatic vs. nonmetastatic disease).
Methods
115 patients with p-NENs and 40 patients from the control group were enrolled. TMs levels, such as cytokeratin 18 (CY18), ferritin, carbohydrate antigen 19-9 (CA19-9), cancer antigen 125 (CA125), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and beta-2-microglobulin (BMG) were determined.
Results
The majority of the patients with p-NENs were non-functional (108/115) and well-differentiated (NET G1 (60/115) and NET G2 (47/115)). TMs levels in the patients with p-NENs were significantly higher than in the control group ($P < 0.01$), except for CA125 and AFP. The area under the curve (AUC) for CY18, CA19-9, and ferritin in patients with p-NENs was significantly higher than in the control group ($P < 0.001$), and their accuracy for detecting patients with p-NENs cases compared to the control group was 68%, 73%, and 77%, respectively. The CY18, CA125, and CEA levels were elevated in metastatic disease irrespective of PNEN grade (M-WU/t, $P=0.01$, $P=0.02$, and $P=0.01$, respectively). The AUC for differentiating metastatic from nonmetastatic disease in p-NENs was < 0.7 in these markers ($P < 0.05$).
Conclusions
The CY18, CA19-9, and ferritin can be used as additional tumor markers in diagnostics patients with p-NENs. The CY18, CA125, and CEA could be useful for diagnostic and prognostic purposes in patients with metastatic disease.

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EP598

Adverse events to mitotane therapy in adrenocortical carcinoma

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Introduction:
Adrenocortical carcinoma (ACC) is a rare tumor, often with an unfavorable prognosis. The management of ACC is challenging due to its low frequency and limited experience. The objective of this study was to describe the adverse events (AE) in patients diagnosed with ACC treated in the Divisions of Endocrinology and Oncology at the Ramón y Cajal University Hospital (Madrid, Spain) in the last seven years.
Methods
Records of patients with ACC from 2016 to 2022 were retrospectively reviewed including clinical and biochemical data, management and follow up. Only patients with available information about mitotane therapy were included.
Results
A total of 8 patients with ACC (4 females and 4 males; median age at diagnosis 51.2 [38.2–73.9] years) were studied, including 4 hormonally inactive, 3 androgen-secreting and 1 cortisol-secreting ACC. All patients underwent surgery. The ENSAT tumor stage was II in 3 patients, III in 1 patient and IV in 4 patients. 2 patients were treated with mitotane in mononotherapy(stage II) and 6 in combination with other treatments (2 radiotherapy, 5 chemotherapy, 1 immunotherapy and 1 lung metastasis surgery). The median duration of mitotane therapy was 8.0 [3.8–38.6]months (4 patients are still under treatment at the time of analysis, 7 January 2023). During follow-up, all patients achieve the therapeutic range after 5.4 [4–6.1]months of treatment, with a median dose of 4.5 [3-5]gr/day and mitotane levels of 15 [12.4–19.7] mg/dl, except one patient due to therapeutic non-compliance. All patients had at least one AE during mitotane therapy. The time to first AE was 23 ± 8.75 days. The most common AE were digestive and hepatotoxicity in 100%, and neurotoxicity in 63% ($n=5$). Considering individually, asthenia, hypercholesterolemia and GGT increase were the most common AE ($n=8$), followed by nausea and anorexia with weight loss ($n=7$). The AE median number was 14 [9–16]. No correlation was found between the number of AE and the mitotane dose when therapeutic levels were achieved ($r=-0.46$,$P=0.251$). Neither with the duration of mitotane therapy ($r=0.32$,$P=0.435$) or mitotane plasmatic levels ($r=-0.32$, $P=0.442$). After a median follow-up of 17.7 [7.4–84.6] months, 2 patients(stage IV) died and 6 are still alive, including 3 with persistent/recurrent disease. There were two patients with ENSAT II stage treated in monotherapy who had to withdraw mitotane due to neurotoxicity. The time to first ACC recurrence/progression during Mitotane treatment was 18 ± 15.93 months.
Conclusions
The most frequent AE with mitotane were digestive, hepatotoxicity and neurotoxicity, which are not associated with the level, dose or duration of mitotane therapy.

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EP599

Treatment with 177Lu-dotatate in metastasic advanced neuroendocrine tumors with positive expression of somatostatin receptors, in a third level hospital in Spain from 2015–2022

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Introduction
^{177}Lu-Oxodotreotide(PRRT-Lu) has the approval by EMA and FDA since 2017 for the treatment of patients with gastro-entero-pancreatic neuroendocrine tumors(GEP-NET). However, in daily clinical practice it has also been used in other NET tumors such as paragangliomas, lung NET, medullary thyroid cancer, and others. The aim of this study is to describe the characteristics and follow-up of patients treated with PRRT-Lu in a third level hospital in Spain from 2015-2022.
Methods
Descriptive and transversal study of 103 patients with NET and positive expression for somatostatin receptors, in advanced stage or progressive disease treated with PRRT-Lu. Characteristics and follow-up of the patients are expressed as media or percentage (SPSSv26.)
Results
– Mean age at treatment was 63 years(SD14). 49.5% were men. PRRT-Lu was administered in 85% NETs, 10.2% PG/PHEO, 0.9% medullary thyroid cancer.
– Primary tumor localization: 36.5% pancreas, 23.4% small intestine, 13.1% lungs, 7.5% suprarenal glands, 8.4% unknown primary.
– The treatment was administered every 8 weeks following standard PRRT-Lu recommendation: 60.7% received 4 doses, 10.3% 3 doses, 9.3% 2 doses, 12.1% 1 dose. 4 patients have been retreated during follow-up.
– 99% of the patients received prior treatments, 87% SSA, 23% chemotherapy, 40.7% everolimus, 23.3% sunitinib. PRRT-Lu was used as 1st line of treatment in 1 patient, 2nd line in 44 patients (42.3%), 3rd line in 75 patients (72.1%), 4th line in 12 patients (11.5%), and as 5th line in 10 patients (9.6%).
– Median follow-up is 17.9 months(IQR 25.6), with a maximum follow-up 68 months. During follow up according to RECIST criteria: 38.3% Stable Disease, 29% progressive disease, 7.5% partial response, and 21% NA (6.5% lost follow-up, 14.5% have just started treatment).
– Adverse effects: 60.7% did not have any adverse event, 11.2% gastrointestinal, 5.6% hematologic, 10% asthenia, all of them G1-G2. Only one patient had a severe adverse event, a medullary aplasia that caused death. Metabolic complications presented with the administration of the medication were: diabetic ketoacidosis, severe hyperkalemia, hypertensive crisis, and uncontrolled VIPOMA crisis.
Conclusion
– Treatment with 177Lu-Dotatate must be considered as a treatment of advanced NETs with positive expression of somatostatin receptors, because of the favorable results in PFS and safety.
– Patients should be assessed within a multidisciplinary committee and framed in Reference Units, given their therapeutic complexity.
– The endocrinologist's role in monitoring the patient must be a cornerstone, in order to detect and treat endocrinological complications before, during and after treatment.

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EP600

Experience with variants of the SDH gene related to paraganglioma in the Southern Health Area of Seville (Spain)

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Introduction
Paragangliomas are rare tumors originated from extraadrenals chromaffin cells. Most are sporadic, but between 30% and 50% are associated with hereditary syndromes. Mutations in the succinate gene dehydrogenase (SDH) have been identified as a cause of the hereditary paraganglioma-pheochromocytoma syndrome.
Material and methods
Descriptive study of case series of patients belonging to the Southern Health Area of Seville with mutations in the SDH gene associated with hereditary paraganglioma syndrome.
Results
There were 22 patients belonging to four different families, who were carriers of genetic mutations in SDH gene. 27.27% (6/22) of them have developed tumors related to these genetic variants. Median age of patients at diagnosis of tumors was 35 years. The heterozygous mutation in exon 2, c.79>T of the SDHB gene was the most frequent, affecting 45.45% (10/22) patients; 3/10 of them (33.33%) presented paraganglioma and 1/10 adrenal hyperplasia. On the other hand, c.293G>A mutation in SDHB gene affected to 5/22 patients (22.72%); 1/5 of them presented paraganglioma. Thirdly, c.761C>T mutation in the SDHB gene affected to 4/22 patients (18.18%); 1/4 of them presented paraganglioma. Lastly, c.1A>G mutation in SDHC gene affected 3/22 patients (13.63%); 1/3 of them developed paraganglioma. All cases were asymptomatic. None was functional and only 1 case presented slightly increased levels of chromogranin A. All cases required surgical treatment and only 1 needed chemotherapy.
Conclusions
– Despite its rarity, we should not forget to include paraganglioma in the differential diagnosis of patients with compatible symptoms.
– Once diagnosed, it is essential to consider genetic tests in order to establish a possible hereditary origin.
– If the hereditary origin is confirmed, it should be considered to extend the study to relatives to diagnose more cases and to supervise carriers of the mutation.

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EP601

An Oestrogen-secreting neuroendocrine tumour in the lung

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Case:
A 59-year-old female with a past medical history of surgically treated primary hyperparathyroidism (PHPT) and breast cancer presented with irregular periods, post-menstrual bleeding, hot flushes, fatigue, and left loin pain. Furthermore, she reported weight gain of approximately 8 lb over 6 months and easy bruising in the absence of antiplatelet and anticoagulant therapy. There were no central, respiratory, or gastrointestinal symptoms. She was normotensive, and the clinical examination was unremarkable. She was established on Tamoxifen therapy. Her father had colonic polyps, while her mother suffered from a uterine malignancy. Initial blood work is detailed in Table 1. For loin pain, the ultrasound scan of the renal tract showed mild dilatation of the right renal pelvis. An overnight dexamethasone suppression test showed undetectable serum cortisol (<30 nmol/l), and a genetic screen for multiple endocrine neoplasia (MEN-1) returned negative. A CT thorax, abdomen & pelvis (CT TAP) showed a left lower lung lobe mass measuring 43 mm with no radiological evidence of metastases. Cranial imaging was unremarkable. The lung mass did not demonstrate FDG uptake on PET CT, and there was no evidence of FDG avid nodal or distant metastasis. It was felt that the lung mass represented an oestrogen-secreting neuroendocrine tumour, and a left lower lobectomy was planned. The biopsy results were deemed unusual and difficult to interpret. The post-operative oestrogen levels were undetectable (Table 2), and patient symptoms resolved. A follow-up CT TAP 6 months post-op showed no new lesions. The patient remains under Endocrinology follow-up with persistently suppressed oestrogen and gradually rising gonadotrophin levels.

Learning points:
1. Significantly elevated oestrogen levels in this age group should prompt clinicians to search for central and peripheral causes.
A systematic approach under MDT guidance is imperative to investigate atypical and vague symptoms of rare pathologies.

Table 1 Initial blood test results

Blood test	Result	Normal range
FSH	10.2 IU/l	25.8–134.8
LH	7.7 IU/l	7.7–58.5
Oestradiol	***4155 pmol/l***	***<505***
TSH	1.9 mU/l	0.27–4.2
PRL	451 mIU/l	102–496
Sodium	142 mmol/l	133–146
Potassium	4.1 mmol/l	3.5–5.3
Urea	4.5 mmol/l	2.5–7.8
Creatinine	70 μmol/l	45–84
Haemoglobin	139 g/l	115–165
Platelets	263 × 10^9/l	150–450

FSH; follicle-stimulating hormone, LH; Luteinizing hormone, TSH; thyroid stimulating hormone, PRL; prolactin.

Table 2 Post-operative blood results

Blood test	Result	Normal range
FSH	24.9 IU/l	25.8–134.8
LH	14 IU/l	7.7–58.5
Oestradiol	***<92 pmol/l***	***<505***

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EP602

Revision of the histopathological examination following 68 Ga DOTA-FAPI-04 PET/CT of a Neuroendocrine breast tumor diagnosed as Invasive Ductal Carcinomatosis initially

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Neuroendocrine tumors (NETs) of the breast are very rare. They represent less than 1% of breast carcinomas. It is important to differentiate metastatic neuroendocrine neoplasia from primary neuroendocrine neoplasia of the breast. Histopathological misinterpretation of a breast NET is common. In a study of 18 NET cases that metastasized to the breast, it was found that 62% of these tumors originated from the gastrointestinal tract and 28% from the lung. Forty-four percent of these tumors were incorrectly diagnosed as primary breast carcinoma We present you a case of a 59-year old female patient who visited the clinic due to occasional vomiting and nausea for the last year. Her examination revealed a breast mass, which had been initially diagnosed as Invasive Ductal Carcinoma by histopathological examination (Figure-1). After that, a Fluorodeoxyglucose (FDG) – Positron Emission Tomography (PET)/Computer Tomography (CT) was ordered to investigate the lesions. But the scan did not reveal any pathology. Subsequently, the patient underwent [68Galium (Ga)]Ga-Fibroblast Activation Protein Inhibitor (FAPI) PET/CT which demonstrated pathological uptake in the mesenteric root and breast (Figure 2-B). Due to the conflicting findings, histopathological examination of the tru-cut biopsy was repeated and it has confirmed the diagnosis of NET (Figure-3). Therefore, 68Ga-DOTATATE PET/CT was performed. Multiple lesions with increased DOTA activity were illustrated in bilateral breast, mesenteric root, bones and liver (Figure 2-C). Consequently, the revised diagnosis of grade 2 NET was confirmed by histopathology. Although the FAPI uptake pattern of NETs is not exactly established, heterogeneous uptake was reported. In addition to that, [68Ga]Ga-FAPI PET/CT's utility in primary and metastatic NETs was previously demonstrated in case reports. It is also important to note that, although [68Ga]Ga-FAPI PET/CT has shown promising results in tumors of epithelial origin, these scans might be non-pathological depending on the tissue of NET. Our case demonstrates very useful information regarding unusual presentations of NETs. In the light of our case and previous research, we strongly believe that after further evaluation and investigation FAPI-PET/CT might have a beneficial role in the management of NETs.

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EP603

Clinicopathological Features of Insulinoma case series

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Introduction
Insulinoma is the most common functional pancreatic neuroendocrine tumor (PanNET), accounting for more than 50% of all cases. Diagnosis of insulinomas may be challenging. In this study, we aim to discuss the clinicopathological features and long-term follow-up results of insulinoma cases followed up in our clinic.
Material and Methods
It is a descriptive and retrospective study of 13 insulinoma cases diagnosed over 10 years. All data of the patients were obtained retrospectively from the hospital registry system and patient follow-up files. 72-hour prolonged fasting test was performed as a diagnostic test. CT, MRI, Ga-68 DOTATATE PET/CT, EUS, and selective arterial calcium stimulation methods were used for insulinoma localization.
Results
The mean age of the patients was 53.9 ± 19.7 years, and the mean age at the time of diagnosis was 52.9 ± 18.2 years. There was only one patient diagnosed with MEN-1 syndrome. The mean time from the onset of symptoms to the diagnosis was 15 (7-27.5) months. Symptomatic hypoglycemia occurred in eight patients in the first 6 hours (61.54%) during the test. Symptomatic hypoglycemia develops in only one patient t (7.69%) after the first 24 hours. The median size of lesions identified radiologically by MRI was 15 (12-24) mm, and 46.2% of these lesions were isolated in the pancreatic tail. Multiple lesions in the pancreas were detected in 15.4% of the cases. Invasion into fatty tissues surrounding the pancreas was detected radiologically in 1 patient and pathologically in 2 patients. Only one of these patients had liver metastases as distant organ metastases at the time of diagnosis. According to WHO pancreatic neuroendocrine tumor classification, 5 patients had grade 1, 4 patients had grade 2 and 1 patient had grade 3 disease. Surgery could not be performed because 2 of 13 patients refused to have surgery. Nine patients who underwent surgery were in remission in the postoperative period and no recurrence was observed during the 31 ± 28 month follow-up. Octreotide LAR was started in one of the patients who did not accept surgery.
Conclusion
In recent years, thanks to non-invasive imaging methods that have increased in parallel with technological developments, it has been possible to diagnose insulinoma cases, most of which are smaller than 2 cm, earlier and to treat them appropriately. Our experience also highlights that Ga-68 DOTATATE PET/CT may be useful when cross-sectional imaging fails to localize the pancreatic lesion.

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EP604

An unusual etiology of primary hyperparathyroidism in a young woman

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Introduction
Parathyroid carcinoma represents a very rare cause of primary hyperparathyroidism. It can be sporadic (most of cases), but also can occur in association with certain syndromes (multiple endocrine neoplasia, hyperparathyroidism-jaw tumor syndrome or isolated familial hyperparathyroidism).
Case report
An 18-year-old woman was referred to the endocrine clinic because of a severe hypercalcemia, detected in the orthopedic surgery department, where she was hospitalized for surgical correction of a frailty right hip and femur fracture. For a few months, she has been complaining of muscle and bone pain (particularly at the left lower limb) and decreased muscle strength; also, her past medical history included a left thyroid nodule and a hypercalcemia of 13.54 mg/dl two years before, that was not further investigated. At admission, she had a PTH of 1157 pg/ml (NV: 15-65), a calcium of 14.7 mg/dl, a low phosphorus (2 mg/dl), and a 25-OH-vitamin D of 21 ng/ml (NV: 30-100), with normal thyroid and renal function. The diagnosis of primary hyperparathyroidism was established. The values for calcitonin and metanephrines were within the normal range, ruling out MEN 2 syndrome. Also, the normal value for chromogranine A and the absence of clinical features of a pituitary adenoma made the MEN 1 syndrome unlikely. A neck ultrasound revealed 2 hypoechoic nodules, one within the left thyroid lobe and another located under the lobe. A neck and thoracic CT scan showed a left lateral cervical, paratracheal, heterogenous mass of 4.313.233.17 cm, possibly a parathyroid tumor. RX scans of the left lower limb revealed brown tumors. An abdominal US was performed and showed kidney stones, without nephrocalcinosis. After fluid therapy for hypercalcemia, it was performed an "en bloc" resection of the left paratracheal mass and left thyroid lobe. The histological and immunohistochemical studies confirmed 3 foci of parathyroid carcinoma, pT3pN0, with vascular invasion, with positivity for the expression of GATA3, chromogranin A, PTH and parafibromin. Also, genetic testing for hyperparathyroidism-jaw tumor syndrome (HRPT2/CDC73 germline mutation) and MEN 1 gene sequencing have been taken into consideration. After surgery, the PTH dropped to 4.46 pg/ml, with a calcium of 10.5 mg/dl. Then, the patient developed "hungry bone syndrome" and hypothyroidism, necessitating high doses of vitamin D and calcium supplements and L-thyroxine substitution. She had a favorable evolution, with fractures consolidation, PTH and calcium within the normal range and without other signs of tumor recurrence at more than 2 years after parathyroid carcinoma resection.

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EP605

Pitfalls in diagnosis and treatment of parathyroid cancer

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Introduction.
Parathyroid carcinoma (PC) is the one of the rarest endocrine malignances and occurs in 0.5–5% of cases among patients with primary hyperparathyroidism (PHPT). Diagnosis of PC can be challenging and often made after surgery or while local or distant metastases detection. We present a case of a patient with a large intrathyroid PC, which was initially identified as a malignant thyroid nodule.
Case report.
59-old caucasian women was diagnosed with 3.2 cm cystic-solid nodule in the right thyroid lobe with irregular margins and increased blood flow in Jun? 2020. FNAB was performed and papillary cancer suggested (Bethesda V). At presentation: TSH – 1.01 mME/ml (RR: 0.4–4.0), calcitonin < 2.0 pg/ml (RR: 0–5), Ca – 3.19 mmol/l (RR: 2.0–2.57), PTH – not defined. Thyroidectomy and central neck lymph node dissection were performed. Intraoperative cytology suggested a follicular neoplasia. Follicular variant papillary thyroid cancer with no signs of lymph node lesion was confirmed histologically (pT3N0M0). Immunohistochemistry was not performed. In September 2020 patient underwent adjuvant RAI ablation (I-131, 3.7 GBq). In February 2022 hypercalcaemia with Ca 3.15 mmol/l (RR: 2.0–2.65), Ca^{2+} – 1.75 mmol/l (RR: 1.12–1.32) was detected and PHPT suspected. PTH – 1424 pg/ml (RR: 12–88) when measured. Neck US, 99mTc-sestamibi parathyroid SPECT scintigraphy, ?ontrast-enhanced Neck and Chest CT showed no evidence of disease in the neck and chest. The hypervascular liver tumor 33 × 23 mm with irregular margins was detected during abdominal CT.
In April 2022 the liver resection (segment VIII) was performed. Severe hypercalcemia before surgery was corrected with intravenous bisphosphonates and cinacalcet. Hungry bone syndrome after surgery confirmed a successful outcome.
Positive immunostaining for GATA-3, CKpan, CD56, PAX8 in the liver tumor, positive immunostaining for GATA-3, CKpan, CD56, PAX8 and negative immunostaining for thyroglobulin and TTF-1 in the primary thyroid tumor confirmed the diagnosis of intrathyroid PC with single liver metastasis 2 years after the initial surgery.
Conclusion.
Our case demonstrates, that cytology and routine histology are poor at distinguishing malignant thyroid and parathyroid tumors. To avoid faults in treatment, it is extremely important to exclude PHPT before surgery in hypercalcaemic patients with suspected thyroid cancer.

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EP606

Leydig Cell Tumor – a Case of Postmenopausal Hirsutism

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Background
Progressive hirsutism and moderate to severe male-pattern balding in women requires exclusion of an adrenal or ovarian tumor.
Case Presentation
A 51-year-old lady presented with excessive hair on her face and lower abdomen of 1 year duration which affected her quality of life. Her menopause started 3 years ago. Her body mass index was 28.6 kg/m^2. She had hair on her upper lip, chin, and lower abdomen; she had a Ferriman–Gallwey score of 18. On examination the patient was normotensive, with male pattern baldness. A hormone profile revealed a markedly elevated serum testosterone of 3.7 μg/l (< 0.47), androstenedione of 6.1 ng/ml (0.35–2.49 ng/ml) and a free androgen index 67% (0.19–3.63%). Cortisol, prolactin, growth hormone and thyroid function tests, glycemic profile were normal. A CT scan of the abdomen and pelvis revealed a 21 mm right ovarian mass and multiple uterine fibroids with normal adrenal glands. The patient underwent total laparoscopic hysterectomy with bilateral salpingo-oophorectomy. Histology confirmed the presence of a Leydig cell tumour, confined to the right ovary, with no malignant features. Post-operatively her androgen levels normalized and symptoms resolved within 10 weeks.
Conclusion
In postmenopausal women with new onset of hirsutism that is severe or rapidly progressive, the possibility of an androgen-secreting tumor must be suspected and detailed history and physical examination, substantiated by focused biochemical and morphological confirmation is necessary.

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EP607

Extra-adrenal adrenocortical cancer (ACC) associated with multiple endocrine neoplasia type 1

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Adrenocortical carcinoma (ACC) is a rare malignant tumour arising from the adrenal cortex, with an estimated annual incidence of one to two patients per million. Ectopic ACCs are extremely rare. They are believed to arise from cortical fragments arrested during embryologic migration and have been found close to the adrenal gland or along the path of gonadal descent. The majority of ACCs are sporadic, however, ACC has been linked with genetic disease processes, including multiple endocrine neoplasia type-1 (MEN-1). We present the case of a 66-year-old lady referred with newly diagnosed diabetes on a background of primary hyperparathyroidism. Examination revealed Cushingoid features and hormonal evaluation confirmed ACTH-independent Cushing's syndrome. 1 mg overnight dexamethasone suppressed 0900 h cortisol was 548 nmol/l [<50 nmol/l] with an undetectable ACTH <3.0 pg/ml (7.2 – 63.3 pg/ml). DHEAS 5.3 μmol/l (0.5–5.6μmol/l) and androstenedione 3.49 nmol/l (1.39 – 9.77 nmol/l) were normal. Testosterone was suppressed <0.4 nmol/l (0.1–1.4 nmol/l). Imaging revealed a 6×6×4.5 cm right-sided presumed adrenal lesion with Hounsfield units >20, a pancreatic lesion [2.5× 1.6 cm], and bilateral pulmonary nodules [0.9×0.8 cm, 0.7×0.6 cm, 0.3 cm]. Right adrenalectomy was performed and histology was consistent with an extra-adrenal ACC [Weiss score 5/9] within the peri-adrenal adipose tissue. The resected adrenal gland was normal. Lung biopsy confirmed metastatic ACC tissue and endoscopic ultrasound-guided biopsy of the pancreatic lesion revealed a pancreatic neuroendocrine tumour which was diagnosed biochemically to be an insulinoma. Genetic assessment confirmed MEN-1. Adrenal lesions in MEN-1 syndrome have significant malignant potential. ACCs are reported in 2.5–6% of MEN-1 patients. This case highlights the importance of screening for MEN-1 in at-risk patients and the need for close clinical follow-up. To our knowledge, this is the first case report of extra-adrenal ACC in MEN-1 syndrome.

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EP608

Mesenteric paraganglioma with a late-onset metastases accelerated after delayed surgery

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Mesenteric paragangliomas are a rare entity; consequently, 20 cases have been reported to date. Although often found incidentally and considered benign, they have potential to metastasize. We present a case of 63-year old man with a 11-year history of the mesenteric paraganglioma. The lesion for the first time had been described on CT scan of the abdomen in 2010. However, the patient was lost to follow-up. In 2021 CT scan, followed by MRI of the abdomen, perfomed due to reccurent abdominal pain, revealed substantial progression of the tumour size (from 7×5×3 cm in 2010 to 13×10×10 cm in 2021). The patient was qualified for laparotomy. Because of difficult localization and risk of non-radical operation, the lesion was only biopted – the histopathological result was consistent with paraganglioma. Hormonal assessment showed significantly elevated urinary fractionated metanephrines. Genetic testing of SDHB/SDHD, VHL, RET, MEN1, MAX mutation was negative. Control CT scan revealed left hydronephrosis secondary to ureteral obstruction by the tumour mass and further slow progression of the tumour size. Preoperatively performed.

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EP609

Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) of pancreas with typical insulinoma presentation

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Introduction
Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN) of the pancreas are composed of two morphologically different components, each representing at least 30% of the tumor: ductal or acinar adenocarcinoma and neuroendocrine neoplasm (NEN). They are extremely rare tumors whose etiopathogenesis and biological behavior are not fully understood. Given its rarity, we describe a case of insulinoma in the context of MiNEN.
Clinical case
A 55-year-old woman with no relevant medical or family history was referred to our department due to symptomatic hypoglycemic episodes with one year of evolution. The episodes were more frequent in the morning, improved after ingestion of carbohydrates, and capillary blood glucose was between 38–55 mg/dL. She denied taking hypoglycemic agents. Physical examination showed BMI 30 kg/m^2 and was otherwise unremarkable. Laboratory evaluation with 12 h fasting was consistent with endogenous hyperinsulinism: glycemia 53 mg/dL, insulin 11.45 μUI/ml (3–25), C-peptide 3.62 ng/ml (0.93–3.73) and anti-insulin antibody was negative. Calcium metabolism and pituitary lab tests were normal. CT scan and MRI did not show neoformative lesions. Ultrasound endoscopy revealed a solid intrapancreatic formation in the body-caudal transition, hypoechogenic, with 8.8 mm, well-delimited and vascularized, with features suggestive of NEN. Given these results, a diagnosis of insulinoma was made and the patient underwent distal pancreatectomy. After the surgery, the hypoglycemia episodes resolved. Anatomopathological examination revealed a MiNEN of the pancreas with 1.5 cm, comprising a G1 NEN (~70%) and ductal adenocarcinoma (~30%) – staging (AJCC 8th edition): pT1aN0. In the remaining pancreatic parenchyma, a 0.3 cm neuroendocrine microadenoma was also identified. The patient is under surveillance at the Endocrinology and Medical Oncology outpatient clinic. One year after surgery, there is no clinical and laboratory evidence of hypoglycemia nor suspicious lesions on FDG-PET scan. Given the presence of two neuroendocrine pancreatic tumors, the patient underwent MEN1 genetic testing, however, results are still unknown.
Conclusion
The follow-up and prognosis of patients with MiNEN are not well understood. There are few cases of pancreatic MiNEN published in the literature, and their presentation is heterogeneous. However, in most of them, the neuroendocrine component is non-functional, and the diagnosis is made in the context of detection of incidental pancreatic lesion or mass effect. In this case, the neuroendocrine component was as insulinoma and the study of endogenous hyperinsulinism preceded the identification of

the tumor. With this exceptionally rare case, we intend to contribute to the body of knowledge about MiNEN, whose approach remains challenging for clinicians.

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EP610

Pulmonary metastases in differentiated thyroid cancer

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Introduction
The incidence of thyroid cancers is increasing; they are considered to have a very good prognosis with good survival The frequency of metastases is 5 to 10%. The most common locations are lung and bone. The morbidity of metastatic disease is related to the initial histological type, tumour mass, location of metastases, age, possible loss of iodine uptake and 18F-FDG uptake
Materials and methods
We collected 25 patients treated for hormone-dependent differentiated thyroid carcinoma with pulmonary metastases. We first evaluated the therapeutic response to radioiodine according to histological factors; age and location of the metastasis Secondly, we evaluated the evolution of these patients: remission or evolutionary progression as well as the transition to a refractory form.
Results
In patients with pulmonary metastases: The predominant histological type is papillary in 76% The average age is 45 years Morphological evaluation reveals micronodular lesions in 53%; infra radiological in 20% and macro nodular in 28% of cases 68% of patients with pulmonary metastases are iodo avid metastases After univariate analysis, papillary histology is significantly more frequent in iodo avid lung metastases and aggressive forms are significantly more frequent in non iodo avid lung metastases Complete biological and morphological responses are significantly more frequent in iodo lung avid metastases Progression to a refractory form is significantly more frequent in patients over 40 years old and in non iodo avid lung metastases
Conclusion
Our results are in agreement with the data of the literature in fact the patients of less than 40 years: having a more frequent infra radiological forms are better responders to the radioactive iodine and a contrario the refractory forms are more frequent in the patients of more than 40 years

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EP611

Body Mass Index and sporadic Medullary Thyroid Cancer: insights from a large series

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Introduction
An increased Body Mass Index (BMI) has been associated with higher prevalence of many cancers, including differentiated thyroid cancer. However, no data have been reported about potential impact of BMI on aggressiveness of presentation and clinical outcome of medullary thyroid cancer (MTC).
Aim
To evaluate the potential influence of BMI on clinical presentation and outcome of MTC.
Methods
We reviewed anthropometric and clinical data of 444 consecutive patients with sporadic MTC, surgically treated at the Endocrine Surgery Unit and followed at the Endocrine Unit of the University Hospital of Pisa, from 2000 to 2019.
Results
At time of surgery, 92/444 (20.7%) patients had BMI $\geqq 30 \times kg/m^2$ (Ob-group) and 352/444 (79.3%) $< 30\ kg/m^2$ (control group). Ob-group patients were significantly older (median 59.5 vs 54.0 years, $P=0.001$), whilemale gender prevalence did not differ (44.6% vs 45.1%, $P>0.4$). Ob-group showed a significantly smaller tumor dimension compared with control group (median 1 cm vs 1.3 cm, $P=0.001$). Particularly,micro-MTC ($\leq$ 1 cm)was present in 50/92 (54.3%) and 136/352 (38.6%), 1–2.5 cm tumors in 25/92 (27.2%) and 137/352 (38.9%), 2.5–4 cm tumors in 16/92 (17.4%) and 52/352 (14.8%) and tumors $>$ 4 cm in 1/92 (1.1%) and 27/352 (7.7%), in Ob-group and control group, respectively ($P=0.006$). MTCs of Ob-group had both significantly lower T and N stage compared with control group ($P=0.019$ and 0.013, respectively). Otherwise, minimal extra-thyroid extension and multifocality did not differ ($P>0.4$). Ob-group patients had significantly lower levels of pre-operative calcitonin compared with control group (median 67.2 vs 123.5 pg/ml, $P=0.036$). After surgery, the follow-up time did not differ between Ob-group and controls (5.2 vs 6.3 years, $P>0.1$). At the end of follow-up, Ob-group showed significantly lower rate of structural disease, compared with control group (12/92, 13%, vs 80/352, 22.7%, $P=0.036$).
Conclusions
At the time of surgical treatment, about 21% of all sporadic MTC patients were suffering from obesity. In our series, patients with obesity had smaller tumors and less metastatic lymph node involvement, probably due to more frequent and careful medical evaluations experienced by these population leading to an early detection of MTC. Moreover, Ob-group had less structural disease at the end of the follow-up confirming the importance of an early diagnosis of MTC.

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EP612

A new pathogenic variant of MEN 1 gene causing pituitary, pancreatic, parathyroid, adrenal and middle ear neuroendocrine tumors

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Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder caused by germline mutations of MEN1 gene, without genotype–phenotype correlation. It is defined as the occurrence of two or more primary neuroendocrine tumors (parathyroid, enteropancreatic, pituitary), or the occurrence of one of the MEN1-associated tumors in family members of a patient with a clinical diagnosis of MEN1. Multiple parathyroid tumors with hyperparathyroidism are the most common manifestation with highest penetrance between 40 to 50 years, followed by pancreatic neuroendocrine tumors. Our patient, 49 years old, had a family history positive for hyperparathyroidism, gastrinoma, pancreatic and adrenal tumor, (his brother), pancreatic tumor, subcutaneous lipomas, (his father), prolactinoma, (his daughter). He was diagnosed with primary hyperparathyroidism at 37 years, submitted in 2013 to parathyroidectomy that revealed three adenomas. In 2014, he was diagnosed with nonfunctioning pituitary macroadenoma. In 2015, an abdominal computed tomography scan revealed pancreatic tumors and bilateral adrenal adenomas which proved nonfunctional at biochemical evaluation. In 2021, IRM showed the gastric wall thickening and superior digestive endoscopy was performed. Gastric biopsy documented gastric neuroendocrine tumor grade 1. He then developed carcinoid syndrome and elevated levels of chromogranin A ($>$2800 ng/ml), serotonin (535.3 ng/ml), and 5-hydroxyindoleacetic acid (17.83 mg/24 h). Functional imaging (99mTcEDDA/HYNIC-TOC SPECT/CT) revealed gastric and pancreatic tumor with high expression of somatostatin receptors, with secondary lymph node and liver involvement, and a faint uptake in the middle ear. To rule out the existence of a phenocopy of this syndrome we analyzed *MEN1* gene by Sanger sequencing. Genetic analysis showed the occurrence of a new heterozygous mutation by the insertion of two nucleotides in exon 3 of *MEN1* gene at the position c.520_521insCA, resulting in a frame shift mutation (H174Pfs*12). This mutation is predicted as pathogenic and disease causing (MutationTaster). One previous report identified a pathogenic missense mutation at the same position, but in our case the alteration is different and not described yet.
We report a patient with a novel mutation in MEN1 gene presenting with primary hyperparathyroidism, a nonfunctioning pituitary macroadenoma, bilateral nonfunctioning adrenal adenomas, neuroendocrine gastric and pancreatic tumors with liver metastases, and middle ear neuroendocrine tumor. A higher risk of aggressive tumor phenotypes has been described in relation to frameshift and nonsense mutations, predominantly associated with aggressive gastroenteropancreatic neuroendocrine tumors (GEP NETs). Patients with aggressive phenotypes and genetically confirmed MEN1 should be carefully followed up in a multidisciplinary approach, preferably at 3 months interval for long-term.

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EP613

A Rare Case; Ectopic ACTH Syndrome Caused by Metastatic Germ Cell Tumor

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Introduction
Although ectopic ACTH syndrome (EAS) is most commonly seen in cancers with neuroendocrine differentiation, it is not a common condition in germ cell tumors. Here we report a rare case of EAS due to metastatic germ cell tumor.
Case report
A 53-year-old male patient presented with fatigue, weakness, swelling in both legs and weight loss for 3 months. He had type 2 diabetes and no history of smoking or alcohol. In the physical examination, there were aphthous lesions in the mouth, widespread hyperpigmentation on the skin and pitting edema of the feet. In laboratory results hyperglycemia, severe hypokalemia and elevation in cholestasis enzymes were observed. Abdominal computerized tomography showed multiple metastatic masses and lymph nodes in the abdomen, the largest of which was in the liver. Needle biopsy of the liver mass resulted in metastatic germ cell tumor metastasis. No focus was detected in the imaging performed for primary focus scanning. Hypercortisolemia was found in the examinations performed due to severe hypokalemia resistant to treatment (Table 1). As a result of further investigations, although ACTH staining was negative in the immunohistochemical examination, the patient was considered to have EAS due to metastatic germ cell tumor, since it was clinically compatible. The patient was started on bleomycin-etoposide-cisplatin-based antineoplastic therapy for metastatic germ cell tumor and a steroid synthesis inhibitor was started for the treatment of hypercortisolemia. After 4 cycles of chemotherapy, the cortisol level was determined as 2.93 μg/dl because the patient had symptoms such as weakness, loss of appetite and hypotension. Adrenal insufficiency developed with the inhibition of steroidogenesis and control of the ACTH secreting focus with antineoplastic therapy. Therefore, the steroid synthesis inhibitor was discontinued and hydrocortisone replacement was started. It was planned to continue antineoplastic therapy until complete remission was achieved.

Table 1 Laboratory findings

Parameter	Result	Reference Range
Cortisol	26.48 μg/dL	
ACTH*	181 ng/l	<46
Mid-night Salivary Cortisol	43.45 ng/ml	0.7–2.2
Urine Free Cortisol	109.53 μg/24 h	3.5–45
2 mg DST** (Liddle test)	20.56 μg/dL	
Overnight 8 mg DST**	16.9 μg/dL	

*ACTH: Adrenocorticotrophic Hormone **DST: Dexamethasone Suppression Test.

Conclusion
When EAS is detected, identification and treatment of the ACTH-secreting focus is important in achieving remission. It should be kept in mind that immunohistochemical ACTH staining may be negative in metastatic foci. This case taught us that the etiology of hypercortisolemia should be addressed with a broad perspective and a multidisciplinary approach.

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EP614

Pan-endocrine cancer pattern of somatic mutations: Toward Genotype–Phenotype correlation and machine learning methods

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Background
Neuroendocrine tumors (NETs) and Adrenocortical carcinomas (ACCs) are rare and heterogeneous tumors entities. Advanced NETs and ACC own poor prognosis with less than 40% of five-year survival. There is a need for improved biomarkers to predict disease prognosis and treatment sensitivity. A broad overview of NETs and ACC genetics has never been explored.
Aim
To investigate genotype–phenotype correlations on a pan-endocrine cancer level with a focus on somatic mutations.
Methods
A litterature search identified papers utilizing Whole Exome/Genome Sequencing on NETs or ACCs since 2000. Key inclusion criteria were: 1. NETs from the gastrointestinal tract, lung, adrenal/paraganglia and thyroid as well as ACC; 2. Available data on patient characteristics and somatic mutations. Data on clinicopathological features and genetic variants were collected.
Results
1747 articles were screened and thirty-four publications were selected. Data from a total of 1209 patients were enrolled in this study. Among ACCs, 264 cases were included. 67.8% (145 out of 214) were females; median age was 49.6 (range,13–83) years; mean tumor size was 11.1 ± 4.9 cm; and 36.2% (76 out of 210) manifested malignant behavior with either local invasion, metastatic or recurrent disease. Among 945 NETs, we identified 304 pheochromocytoma/paraganglioma, 131 medullary thyroid carcinoma, 249 pancreatic NETs, 182 small intestinal NETs, 61 lung NETs, 6 breast NETs, 6 duodenal NETs and 6 unkonwn orign NETs. Among these, 50.3%(306 out of 608) were female patients. The median age was 52 (range,10–89) years; mean tumor size was 4.4 ± 2.6 cm and 35.6% (217 out of 609) were recorded with malignant behaviors.
Conclusion
This cohort may provide a first and broad overview of the genetic landscape among both NETs and ACCs. Future research will aim to identify genotype–phenotype correlations with a focus on the dicsocery of prognostic biomarkers.

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EP615

A case report – Should we start breast cancer screening earlier in the MEN-1 patients?

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Multiple endocrine neoplasia type 1 (MEN-1) is characterized by an increased predisposition to the development of tumors of the endocrine tissues, such as parathyroid glands, anterior pituitary, and duodenopancreatic neuroendocrine tumors. It is an autosomal dominant disorder due to germline mutations in the MEN-1 tumor suppressor gene. This gene encodes the menin protein, which is involved in cell growth and differentiation, and in sensing or repairing DNA damage. We present the case of a patient whose diagnosis of MEN-1 syndrome was made incidentally during staging for breast cancer. The patient is a female, 43 years old, with no relevant personal history, and a family history of consanguinity – the patient's parents are brother and sister. During the staging for breast cancer, the patient underwent breast mammography and biopsy after the detection of a 25 mm nodule in the right upper-external breast quadrant. The anatomopathological evaluation revealed invasive ductal carcinoma. Then, a genetic test was performed identifying a breast cancer pathogenic variant (CHEK2 c.1141 A>G VUS) and, incidentally, a MEN-1 pathogenic mutation (c.1117G>A). After the identification of the MEN-1 mutation, the patient was referred to an Endocrinology consultation. The initial laboratory evaluation accordingly to Clinical Practice Guidelines for MEN1 revealed no preliminary abnormalities: plasma calcium 9.3 mg/dl, albumin 4.2 g/dl, PTH 63.6 pg/ml, gastrin 23 pg/ml, glucagon 145 pg/ml, vasointestinal polypeptide 14 pmol/l, chromogranin A 7.3 nmol/l, insulin 16.0 μUI/ml, with an associated fasting glucose level of 90 mg/dl, prolactin 6.5 ng/ml, IGF-1 92 ng/ml, TSH 1.71 mUI/l, fT4 14.2 pmol/l, FSH 23.1 mUI/l, LH 7.6 mU/l, 17-Beta estradiol 80.6 pg/ml, ACTH 10.7 pg/ml, CA 125 11.7 U/ml. Imaging evaluation done during staging for breast cancer (including gynecological echography, thorax MRI and bone scintigraphy) showed no evidence of disease other than the referred nodule. There is growing evidence that MEN-1 increases the risk of development of breast tumors by at least two- to threefold (in frequency and in age of appearance) and several MEN-1 studies suggest the age of 40 years for the start of screening. However, Clinical Practice Guidelines for MEN-1 do not mention breast cancer and do not suggest changes in breast cancer screening compared to the general population. Since in Europe, the majority of countries conduct breast cancer screening programs starting at age 50, this case raises the question – Shouldn't we start breast cancer screening earlier in the MEN-1 subpopulation?

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EP616

Posterior reversible encephalopathy syndrome (PRES) as a presentation of a metastatic pheochromocytoma (PHEO)

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Introduction
PRES it's a neurologic syndrome with multiple manifestations, that includes high blood pressure with a variable range. It usually develops in the context of medications or an underlying condition. The treatment is usually symptomatic and determined by said disease.

Objective
We present the case of a patient with PRES linked to the diagnostic of a metastatic PHEO.
Case-report
A 72-year-old male underwent left adrenalectomy in 2016, because of a PHEO. Pathology findings included capsular invasion, necrosis, diffuse focal pattern, and nuclear pleomorphism without invasion of the perinephric fat. He had no evidence of disease until 2020, when he lost follow-up because of COVID-19 pandemic. In May 2022, he was admitted in Neurology because of a hypertensive crisis up to 205/97 mmHg, headache, an acute confusional state and transient cortical blindness, that lasted hours, compatible with PRES. He was discharged with hypertensive medication. He was readmitted in June 2022 because of deterioration of general condition and weight loss up to 10 kg. Computed tomography (CT) of the chest, abdomen and pelvis was performed, showing multiple pulmonary, pleural, hepatic and bone lesions, without clear evidence of primary tumor. Because of the history of the patient and symptoms presented in the previous hospitalization, 24 h catecholamines and fractionated metanephrines urine test was determined, presented in Table 1 After the results, we initiated and titrated alpha-blockade with Doxazosin until we achieved adequate blood pressure. We completed the study with 123I-Meta-Iodobenzylguanidine Scintigraphy and Ga-68 DOTATATE PET/CT Scan which revealed increased uptake in the CT lesions. Lanreotide 120 mg sc was initiated and after nuclear imaging was performed, radionuclide therapy was also initiated, but the patient presented liver failure and died after the 1st dose of Lutetium-177.

Table 1 24 h catecholamines and fractionated metanephrines in urine

	RESULTS (g/24 h)	NORMAL RANGE
Norepinephrine	**955.3**	**[23–105]**
Epinephrine	**69.9**	**[0.5–20]**
Dopamine	**9.678**	**[65–400]**
Normetanephrine	**195.379**	**[162–528]**
Metanephrine	**22.263,52**	**[64–302]**
3-Methoxytyramine	**60.522**	**[94–400]**

Conclusions
Even though neurologic complications are rare, in the presence of PRES or other atypical cerebrovascular symptoms, PHEO should be suspected. PHEO should have a lifelong follow-up to prevent complications and early detection of recurrence/malignancy.

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EP617

Molecular predictors of response to the therapy with mitotane in adrenocortical cancer

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Background
Adrenocortical cancer (ACC) therapy is characterized by insufficient effectiveness. Currently, mitotane, an adrenolytic drug, is the only drug approved for treatment of ACC and is used in the adjuvant setting and in case of metastatic or advanced disease. However, the administration of mitotane to certain groups of patients remains controversial due to the low response rates, high toxicity and limited data on the benefit of treatment. Expression levels of the large subunit of ribonucleotide reductase M1 (RRM1), cytochrome P450 2W1 (CYP2W1) and sterol-O-acyltransferase-1 (SOAT1) are considered as potential predictors of response to mitotane therapy. The aim of this study was to estimate the immunohistochemical expression of RRM1, CYP2W1 and SOAT1 in ACC as markers of clinical outcomes and response to the therapy with mitotane.
Methods
The study included 62 patients older than 17 years of age with a diagnosis of ACC confirmed histologically and immunohistochemically. Pathomorphological examination of surgical and consultative material from patients treated between 2005 and 2020 in Endocrinology research center and other health care centers of Russia was performed. Antibodies to SF-1, Ki-67, RRM1, CYP2W1, SOAT1 were used diluted in accordance with recommendations of firms-manufacturers for immunohistochemical detection. Kaplan–Meier method was used to estimate disease-free survival (DFS) and its predictors.
Results
Mitotane therapy was initiated in 29 patients in the postoperative period, the control group comprised 33 patients according to results of immunohistochemical examination (level of expression of Ki-67). In the control group of patients with low and moderate RRM1, CYP2W1 and SOAT1 immunoreactivity, a better DFS was observed ($P=0.037$, $P=0.020$ and $P=0.001$, respectively) compared to the study group at this level of marker expression. In case of high expression levels of the markers, no statistically significant differences were found.
Conclusion
In this study we have identified tendences in the correlation of the expression of potential prognostic markers and DFS in our sample of patients. Evaluation of RRM1, SOAT1 and CYP2W1 immunoreactivity opens new possibilities for personalized mitotane therapy in ACC.

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EP618

Merkel cell carcinoma, experience of a single center

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Introduction
Merkel cell carcinoma is a rare and aggressive neuroendocrine skin cancer. It is characterized by a high rate of local recurrence after surgical resection as well as the occurrence of distant metastases. It mostly occurs in the elderly and the exact etiology is unknown. The most significant risk factors for its occurrence are exposure to ultraviolet light and the oncogenic effect of the Merkel cell polyoma virus.
Aim
Demographic and clinical characterization of patients with Merkel cell carcinoma as well as tumor characteristics and their impact on the outcome of the disease.
Methods
The retrospective study included 37 patients diagnosed with Merkel cell carcinoma who were treated in our department between 2001 and 2022.
Results
Most patients were male, 64.9%, while the average age at the time of diagnosis was 62.03 ± 12.03 years. The median follow-up of patients from the time of diagnosis was 24 (5–121) months. The primary site of the tumor was unknown in 32.4% of patients, while localization in the head and neck, upper extremities, lower extremities, and glutes was 12.9%, 19.4%, 12.9%, and 16.1%, respectively. Metastatic disease at the time of diagnosis was verified in 64.9% of patients, most often in locoregional lymph nodes 61.1%. In stage I the disease was diagnosed in 17.1% of patients, in stage II in 14.3%, stage III in 57.1% and stage IV in 11.4% of patients. Systemic chemotherapy was used in 82.9%, locoregional radiation therapy in 34.3%, and immunotherapy in 16.2% of patients. Survival was statistically significantly shorter in patients with stage III and IV disease compared to patients with stage I and II disease (P 0.04). The earliest death occurred 5 months after diagnosis. A trend in shorter survival was observed in male patients (P 0.06).
Conclusion
Advanced Merkel cell carcinoma is associated with a worse prognosis. The fact that in most patients at the time of diagnosis there is locoregional dissemination of the disease imposes the need for a greater degree of clinical suspicion among doctors of various specialties, as well as raising public awareness of this type of cancer with the aim of early diagnosis and treatment.

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EP619

Malignant Struma Ovarii: Report of Two Cases Diagnosed with Follicular Variant Papillary Thyroid Carcinoma

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Introduction
Malignant struma ovari is a rare ovarian mature teratoma. The diagnosis can be done histopathologically. There are no specific diagnostic findings in terms of imaging, clinical and laboratory. We present two cases of malignant struma ovarii in papillary follicular variant subtypes in this report.
Case report
Case 1; The patient was a 44 year old female, she had complaints of pelvic pain and a palpable lower abdominal mass. Pelvic MRI examination showed a semisolid mass of $90 \times 80 \times 103$ mm in the left ovarian region. Tumor markers

and thyroid tests were normal. Laparotomy was performed. Left salpingo-oopherectomy material was sent for frozen section and was reported to be malignant. Right salpingo-oopherectomy and total abdominal hysterectomy were performed. Histopathology results showed as follicular variant papillary thyroid carcinoma. There was minimal invasion in the tumor capsule. Thyroid ultrasonography examination showed a hypoechoic nodule without blood supply with measuring 3.5×3×3.5 mm. Total thyroidectomy followed by radioactive iodine treatment was offered for the patient. However the treatment could not be continued because the patient was out of follow-up.

Case 2; A 37 year old female, she had complaints of pelvic pain in the left lower quadrant and distention. Pelvic MRI examination showed two masses of 91×60×73 mm and 34×35×40 mm in the left ovarian region. Left salpingo-oopherectomy were performed. Histopathologic examination showed follicular variant papillary thyroid carcinoma in the struma ovari. Right salpingo-oopherectomy and total abdominal hysterectomy were performed. Thyroid ultrasonography examination and thyroid tests were normal. Total thyroidectomy followed by radioactive iodine treatment was offered for the patient. The patient was referred to general surgery for thyroidectomy.

Conclusions

Due to the rarity of malignant struma ovari and the lack of adequate case series, diagnosis and treatment are unclear. Bilateral salpingo-oopherectomy, total abdominal hysterectomy and I 131 ablation after thyroidectomy reduce the risk of recurrence and facilitate patient follow up with thyroglobulin.

Keywords: Malignant Struma Ovari, pelvic pain, thyroidectomy

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EP620

Clinical Case: Missed Diagnosis of Poorly Differentiated Thyroid Cancer

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Introduction

Poorly differentiated thyroid cancer (PDTC) is a rare subtype of thyroid carcinomas, that diagnosis is difficult and often missed in daily routine. It is believed that most of them arise in well-differentiated thyroid carcinoma, although a subset of these lesions apparently also arise de novo.

Case report

In 2007, a 55-year-old man had a total thyroidectomy and received radioactive iodine treatment post-surgery due to well-differentiated papillary thyroid carcinoma (PTC) (pT2N0M0). An endocrinologist examined the patient several times for a possible recurrence of thyroid cancer, but there were no signs: thyroglobulin (TG) was <0.1 μg/l. The patient is currently on thyroxine replacement therapy (targeted thyroid-stimulating hormone <0.1 mIU/l). In 2019, an elevated TG level was detected (6.47 μg/l), and an ultrasound (US) of the neck showed a calcified lymph node in the III zone of the right side. Fine-needle aspiration of the calcified lymph nodes revealed any tumorous alterations and TG did not increase dynamically (4.5 μg/l). In 2020, the patient complained of pain in his left upper arm. A CT scan revealed a pathologic humeral fracture, and a bone tumor biopsy indicated PTC metastasis. CT scan of the neck, chest, abdomen, and pelvis revealed no primary tumor, therefore the right lung root and bronchopulmonary lymph nodes were more likely to be pathological, likewise, a blood test found an elevated TG level (637.5 μg/l). Hence, the humeral tumor was excised, followed by fracture fixation and cementoplasty; the histology of the tumor confirmed PTC metastasis in the bone. The patient was given radioactive iodine therapy in ablating dosages following surgery. Four months after, a CT scan shows slightly enlarged peribronchial and bronchopulmonary lymph nodes, and TG level increased over time up to 716.05 μg/l. After biochemical and radiological progression along with radioactive iodine resistance, the patient's medical records and cytological features were reviewed – PDTC was diagnosed. Kinase inhibitors have been initiated for cancer treatment (Lenvatinib). In 2022, on a CT scan, the disease has not progressed, and the level of TG has decreased (217 μg/l), indicating that the cancer is likely responding to biological therapy. This year, the patient feels better and has started the 20th cycle of Lenvatinib.

Discussion

PDTC accounts for 2–15% of all thyroid malignancies, consequently, PDTCs, which require a correct diagnosis in order to receive adequate treatment, are often missed in daily routine. In our case, a correct diagnosis was made 13 years after the PTC diagnosis.

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EP621

Systemic manifestations of medullary thyroid cancer

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78-year old previously healthy man was reffered to Outpatient endocrinology clinic due to painful spine and shoulders. His lumbar and thoracic X-ray showed decreased lumbar and thoracic vertebrae (L1, L2 and Th 5) and densitometry indicated slightly decreased bone density with T score -1,0 in left femoral neck and L1 vertebra. Since patient mentioned recent unintentionally 10 kg weight loss he was processed to further work-up and additional blood tests were done. Secondary osteoporosis was ruled out. Levels of testosterone and cortisol as well as PTH, calcium and phosphate were normal. Slightly elevated PSA (6 μg/l) and significantly eleveted CEA 75.2 μg/l (n.v.< 5) were noticed, and TSH was 8 mIU/l. Patient had no history of thyroid disease earlier. Thyroid ultrasound showed hypoechoic nodule with smooth irregular capsule size 2.3×2.4×1.7 cm in right lobe and FNA was done. Cytological finding indicated medullary thyroid carcinoma. Neck ultrasound was repeated to evaluate lymph nodes and FNA of largest ipsilateral lymph node size 8×5 mm with visible hilus and reactive aspect was done preoperatively – no tumor cells were found. Additonal measurement of serum calcitonin and urinary fractionated metanephrines was done. Calcitonin was extremely high, 1998 ng/l (n.v. 8,31–14,3) and pheochromocytoma was ruled out. Since very high levels of serum calcitonin and CEA were found, CT of thorax and abdomen was done and no metastasis were found. Patient underwent total thyroidectomy with cervical lymph node dissection. Patohistology confirmed medullary thyroid carcinoma with 4/16 positive lymph node on ipsilateral site, contralateral lymph nodes were not positive for tumor. Postoperatively values of calcitonin was 10×05 ng/l (n.v. 8,31–14,3) and CEA was 31.8 ng/ml, but since postive lymph nodes patient was reffered to oncologist. According to current NCCN guidelines, after diagnosis of MTC was confirmed, screen for germline RET proto-oncogene mutations was done. It showed that patient had mutation c. 790 in 13. exsone of RET gene which is related with MEN2 syndrome. In conclusion, paraneoplastic syndrome is not so rare with MTC – literature refers flushing and diarrhea as most, and ectopic secretion of ACTH as less common. I wanted to show patient with systemic manifestation not commonly described with MTC as were weight loss and bone pain in patient whose age would not indicate thyroid tumor to be cause of these symptoms.

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EP622

Primary multiple carcinomas: Papillary thyroid carcinoma and primary neuroendocrine liver carcinoma

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Liver neuroendocrine carcinoma is a relatively rare disease. There is lack of description due to prognostic information of the disease. Liver serves as an visceral organ, taking part in several endocrine functions, according to an investigations has produced specific proteins and activate thyroid hormones, glucocorticoids. This article describes clinical case of 54 years man with clinical diagnosis of Grave's disease. Liver examination showed normal liver hormones, radiology investigation revealed a nodule (size of the nodule 7.0–5.6 cm) localization in the right lobe of liver. Patient has no diagnosis of Hepatitis C virus, AFP was in normal range. According to liver postsurgical investigation the low Grade neuroendocrine carcinoma revealed. There are extremely rare cases of primary liver neuroendocrine carcinoma. Following our recommendations patient examined due to excluded metastatic lesions (colonoscopy procedure) and was revealed without tendency of cancer in the intestines. According to immune profile and histological examination neuroendocrine liver carcinoma Grade 1 revealed. Patient followed with thyroidectomy a year later with diagnosis of papillary thyroid microcarcinoma with multi centric growth and tendency in pre- and paratracheal lymph nodules (2 nodules). According to the literature, liver neuroendocrine carcinoma – Grade 1 don't characterized with aggressive behavior. Therefore in such case, liver neuroendocrine carcinoma metastasis developed in the retroperitoneum after thyroidectomy, three months later. Neuroendocrine liver cancer is more aggressive in association with papillary thyroid cancer. As a conclusion there are rare cases of primary multiple carcinomas associated with papillary thyroid microcarcinoma in the literature, and this article is an example of aggressive follow up of Primary Multiple

Carcinomas: liver neuroendocrine cancer with association of Papillary Thyroid Cancer.

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EP623

Head circumferences measured during developmental monitoring visits before diagnosis of pediatric craniopharyngioma

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Craniopharyngiomas (CP) are congenital, benign, embryonic malformations which arise from ectoblastic remnants of Rathke's pouch and are located in the (supra-)sellar region. Many patients show a reduced growth rate and an increased BMI early before the diagnosis of CP. However, it is unknown whether patients with CP present with increased head circumference before diagnosis. A cohort of 90 patients was screened for medical records of their developmental monitoring visits. In 83 patients, data on head circumferences was available. We observed that CP patients with hypothalamic involvement of their tumor tend to have an increased head circumference SDS before CP diagnosis. When comparing head circumference SDS before diagnosis at defined time points between birth and four years of age, all head circumferences were in the upper normal range. However, no statistically noticeable differences were found, comparing hypothalamic involvement and no hypothalamic involvement of the tumor. Congenital embryonic malformations such as CP located in the parasellar area can have impact on cerebrospinal fluid circulation and lead higher head circumferences due to hydrocephalus early before diagnosis. Our results show, that head circumference SDS could be an effective early-indicator for CP. A standardized procedure for head circumference measurements during developmental monitoring visits should be implemented in clinical care. We anticipate that our study is the starting point for prospective studies with larger sample size to assess the potential predictive value of head circumference measurements for an early CP diagnosis.

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EP624

Factors associated with dysglycemia and its post-surgical resolution in patients with Pheochromocytomas and Paragangliomas

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Background
Pheochromocytomas and paragangliomas (PPGLs) are a group of rare neuroendocrine tumors. Dysglycemia has been observed in patients with PPGLs in some small case series. However, few large studies, and none in China, have described the outcomes of dysglycemia after resection, and the factors associated with the development and resolution of dysglycemia in patients with PPGLs.
Methods
We retrospectively analyzed the clinical data of consecutive patients with PPGLs admitted between January 2018 and June 2020. Clinical characteristics were compared between patients with and without dysglycemia. Multivariable logistic regression analysis was used to identify independent predictors and the receiver operating characteristic curves was used to evaluate the diagnostic performance of the variables.
Results
Among 163 patients in this study, 47.9% had preoperative dysglycemia. Patients with dysglycemia were older at diagnosis and have a higher proportion of hypertension. The white blood cell counts and 24-hour urinary epinephrine (24hU-E) concentrations were higher in patients with dysglycemia. Multivariable logistic regression analysis showed that age [odds ratio (OR), 1.040; 95% confidence interval (CI), 1.011–1.070; $P = 0.006$], hypertension (OR, 3.318; 95% CI, 1.375–8.009; $P = 0.008$), and 24hU-E concentration (OR, 1.013; 95% CI, 1.005–1.022; $P = 0.016$) were independent risk factors of preoperative dysglycemia. Taking age, hypertension and 24hU-E into account in the same model, the area under the receiver operating characteristic curve of the model for predicting preoperative dysglycemia was 0.737. The proportion of patients with dysglycemia was significantly decreased after surgery ($P < 0.001$) and patients with postoperative dysglycemia in remission had larger preoperative tumor diameters ($P = 0.005$).
Conclusion
Dysglycemia affects almost half of patients with PPGLs. Age, hypertension, and 24hU-E concentration are independent risk factors of preoperative dysglycemia. Removal of PPGLs can improve dysglycemia in most patients, and the postoperative remission of dysglycemia is associated with the preoperative tumor diameter. These results are of great importance for risk assessment and selection of optimal therapy of dysglycemia in patients with PPGLs.

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EP625

Insulinoma: 4 case reports

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Background
Insulinoma is a rare variety of endocrine neoplasm and is usually benign, solitary, and small in size. It is responsible of endogenous insulin secretion resulting in development of symptoms of hypoglycemia.
Case presentation
We report 4 cases of insulinoma that were diagnosed and managed in the year 2022. Three women and one man aged respectively 76, 68, 60 and 42 years-old. All patients presented a long history of various adrenergic symptoms of hypoglycemia and one patient presented signs of neuroglycopenia including behavior changes and confusion. The mean duration of the symptoms was 8.7 years. Three patients presented spontaneous hypoglycemia with a mean plasma glucose levels of 0.3 g/l concomitant with inappropriately high insulin and C-peptide levels. The positive diagnosis was made in one patient after an 8 h fasting test. The tumors were located preoperatively in 3 cases using pancreatic MRI which have objective a unique nodule in all cases with a mean size of 2 cm. in one case, abdominal CT scan, pancreatic MRI and endoscopic ultrasonography were practiced but the tumor was not located. All patients underwent laparotomies and the tumors were localized peroperatively. Enucleation of the nodules were practiced and all the tumors turned out to be benign after histopathological examination. Symptoms disappeared postoperatively in all cases and the glucose plasma levels were normal.
Conclusion
Insulinomas are rare endocrine tumors that can be life-threatening by causing severe hypoglycemia. Clinical manifestations are diverse and the diagnosis is usually delayed. Biochemical diagnosis is easy, but the preoperative localization of the tumor can be challenging. Surgical resection of the tumor is the treatment of choice and should be done by an experienced surgeon. Risk of reoccurrence is rare after surgery and it usually concerns tumors with high histological grade.

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EP626

Large bilateral adrenal masses: interest of plasma LDH measurement to detect adrenal lymphoma

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Large adrenal masses are strongly suggestive of malignancy. Nevertheless, bilateral adrenal masses are less common (around 20% of incidental adrenal lesions). Metastases and lymphoma are more frequent (especially when aging), and not so easy to differentiate on CT or MRI. Simple biological markers, such as plasma LDH or beta2microglobulin, could help.
Case report
A 69-year-old patient was admitted for abdominal pain with progressive lethargy. Abdominal CT revealed heterogeneous necrotic bilateral adrenal lesions, measuring over 70 mm, invading the left diaphragmatic pillar and the gastric wall. Spontaneous density was above 10HU and wash out negative. Adrenal insufficiency was confirmed by low 0800 h cortisol and increased ACTH. After

ruling out pheochromocytoma, oncologists decided of adrenal biopsy before receiving increased levels of β2microglobulin and LDH. Adrenal biopsy diagnosed non centrogerminative diffuse large B cell lymphoma. In situ hybridization analyses showed a BCL6 rearrangement without BCL2 or MYC rearrangements. An 18FDG PET-CT revealed splenic invasion and multiple lymphadenopathies, which would have been easily accessible to biopsy. Further evaluation revealed marrow infiltration on bone marrow biopsy and a high risk of central nervous system invasion. Overall the age adjusted IPI score was 3 and CNS-IPI score was 6 (high risk). These conclusions led to 8 cycles of R-CHOP21 immuno-chemotherapy plus two cycles of high dose methotrexate regimen in conjunction with intrathecal methotrexate. Treatment was well tolerated and lead to complete remission on PET-CT, CT scan and bone marrow biopsy, still lasting 2 years after the end of treatment.

Discussion and conclusion

When facing bilateral adrenal incidentaloma, lymphoma must be evoked more commonly than with unilateral masses. Adrenal imaging (either CT, PET-CT, or MRI) or existence of adrenal insufficiency, have a limited role in guiding to etiology. Biopsy of adrenal mass is an exposed action that may lead to complications (hemorrhage, sepsis, tumor dissemination) or unhelpful conclusion due to necrosis. Therefore, simple markers such as LDH (and possibly other markers including beta2microglobulin) should be measured to suggest lymphoma (increased in over 70% of cases), and further lead to a screen (by CT and PET-CT if not obvious clinically) for associated lymphadenopathies which are much easier to biopsy than the adrenal gland or for lesions with a higher standardized uptake value which are more commonly conclusive for the pathological diagnosis of lymphoma.

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EP627

A case of synchronous association of stomach neuroendocrine tumor and pernicious anemia

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Introduction

Biermer's disease is a chronic inflammatory disease due to antibodies targeting parietal cells and intrinsic factor compromising vitamin B12 absorption leading to pernicious anemia, and gastric acid secretion leading to achlorhydria. Neuroendocrine tumors are rare neoplasms that have been reported during the evolution of chronic gastritis. We here describe a case of a type 1 gastric neuroendocrine tumor discovered alongside with Biermer's disease.

Case presentation

A 60-year-old patient with no medical history was first diagnosed with anemia. Hemoglobin levels were initially at 9 g/dl with macrocytosis, low levels of vitamin B12 and presence of intrinsic factor antibodies. Since the diagnosis of Biermer's disease was made, a lifetime vitamin B12 supplementation was prescribed. A gastroscopy was performed showing a 4 mm polyp in the gastric mucosa. Histopathology revealed a type 1 stomach neuroendocrine tumor. Since the tumor is well differentiated and nonfunctioning tumor, our decision was to follow up the patient and to monitor him by gastroscopic surveillance.

Discussion

Type 1 neuroendocrine tumors are known to occur in the setting of chronic autoimmune gastritis. Deprived gastric acid secretion due to parietal cell destruction results into continuous gastrin secretion leading to hyperplasia of both G cells and enterochromaffin like cells that could further induce gastric neuroendocrine tumors. Synchronous association of stomach neuroendocrine tumor and Biermer's disease is possible and clinicians should be aware of that.

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EP628

Pancreas, An Unusual Metastatic Site In A Long-term Indolent Surviving Case, Under Somatostatin Analogues Therapy, Of Medullary Thyroid Carcinoma: A Case Report And Review Of Cases Documented In Literature

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Medullary thyroid carcinoma (MTC) accounts for 1%–2% of thyroid cancers and has a variable clinical course. MTCs present with locoregional metastasis in 50% of patients and distant metastasis in 10% to 15% at the time of initial diagnosis. The lungs, liver, and bone are common metastatic sites, and distant metastasis is known to be a poor prognostic factor for long-term oncologic outcomes. We present the long course case, under somatostatin analogues (SSA) therapy, of a 72 years old woman, who underwent total thyroidectomy surgery for multinodular goiter in 2000 with subsequent histologic diagnosis of MTC RET wild type and histologic typing in 2022 of a pancreatic metastasis from known medullary thyroid carcinoma. Since 2005 she was treated with lanreotide autogel (ATG) 120 mg/every 28 days. In 2014 lanreotide ATG was administered with high frequency (every 14 days) for radiological progression. The use of SSA instead of tyrosine kinase inhibitors (TKI) was preferred in light of the symptom-free clinical condition. This case constitutes, to our knowledge, the seventh reported case of pancreatic metastasis from MTC in the literature and we performed a review of the other reported clinical cases. The present report is also significant given the few described recurrent MTC cases in a patient with clinical stable disease with slow radiological progression after surgery and under long-term SSA therapy. This case may suggest that prolonged SSA therapy is beneficial in MTC asymptomatic patients with slow radiological progression; further confirmatory evidence is required.

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EP629

A retrospective study investigating the potential relationship between obesity and thyroid cancer

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Thyroid cancer is the most common endocrine malignancy, and accounts for between 5 and 10% of thyroid nodules biopsied in endocrine services. As per the Global Cancer Observatory, the incidence of thyroid cancer in Bahrain is 2.12 cases per 100 000 people, which is less than the neighbouring countries of Saudi Arabia and Kuwait. The purpose of the study is to investigate the relationship between thyroid cancer and obesity in Bahrain, where 28.9% of males and 38.2% of females are classified as obese. Other risk factors such as radiation exposure and genetics will not be explored from lack of data, but height and iodine concentration in the water will be explored. The study will also include the mode of presentation, histological subtypes, and management of thyroid cancer. The study is a retrospective cohort study of 179 patients who have been diagnosed with thyroid cancer and discussed in the National Tumour Board from the years 2019 to 2021. Access to their E-Files was granted by the Bahrain Oncology Centre. The population consistent mostly of Bahraini females with an age range of 18–88. Most of the study population (41%) presented with an asymptomatic neck swelling which was then investigated and diagnosed as thyroid cancer. The most common histological type of thyroid cancer in our study was papillary thyroid carcinoma (88%). The TNM staging showed that most of our patients had a T1 score, with 60 having N1 score and 9 having M1. Our results show that most of the patients with thyroid cancer ($n = 33$) had a body mass index (BMI) of 25–29.9 and only 25 patients had a BMI of 30–34.9. In previous studies obesity has been thought to contribute as a causative agent in 20% of cancers such as breast and colon. But in our study, we did not find a strong relationship between BMI and the tumour size. However, we were able to show a relationship between increasing age and metastatic disease. And finally, the vast majority of the patients in our study had BMI of overweight rather than morbid obesity. Currently, we are investigating a potential relationship between height and thyroid cancer, as well as low iodine levels in the water supply in Bahrain as possible etiological factors. Unfortunately, genetic studies are not available from our oncology service as part of the work up for thyroid cancer in Bahrain.

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EP630

Angiosarcoma of the thyroid: a case report

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Introduction
Angiosarcomas are aggressive malignant tumors but very rare especially when they are located in the thyroid, characterized histologically by their vascular differentiation and their polymorphic appearance.
Observation
We report the case of a 68-years-old female patient, from a mountainous region who has a history of cholecystectomy in 2018, she underwent a total thyroidectomy for a compressive goiter, the postoperative period was marked by an hypoparathyroidism which was substituted. The anatomopathological examination of the surgical specimen showed a thyroid localization of an angiosarcoma of 5 cm of large axis with extension to the fatty and muscular tissue around the thyroid. The CT scan which was performed two months after the surgery showed a left later tracheal formation measuring 9×5 cm suggesting a recurrence. Adjuvant radiotherapy was proposed to our patient.
Discussion
Angiosarcoma of the thyroid is a rare but very aggressive tumor. it affects more women than men with a sex ratio of 9/3 and an average age of 69 years. These tumors were initially described in the inhabitants of alpine regions where their frequency varies between 2 and 10% of all malignant thyroid tumors. This predilection for mountainous regions has been explained by the iodine deficiency leading to goiter, however, the existence of cases in non-mountainous regions without associated goiter suggests that there are other etiological factors not yet known. These tumors are most often revealed by a rapidly growing cervical mass that may be accompanied by signs of compression, as they can be revealed by metastases in particular pulmonary. Local recurrence and metastasis are frequent and early. The prognosis is poor and the average survival is 9 months.
Conclusion
Thyroid localization of angiosarcoma is exceptional but possible. The therapeutic difficulty is correlated to the frequency of recurrence and its metastatic nature.

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EP631

The role of 131I whole body scan in post-operative assessment of patients with thyroid microcarcinoma

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Introdutcion
In recent years, thyroid microcarcinoma (TMC) predominates in the context of diagnosis and treatment of thyroid cancer. TMC has an excellent prognosis, its management is changed in the last few years, reducing surgical procedure and role of radioiodine ablation (RAI). Therefore, the question is what tests have a diagnostic value in patients with thyroid microcarcinoma after thyroidectomy
The aim of this study was to evaluate the role of 131 I whole body scan (WBS) in post operative assessment of patients with TMC.
Materials and methods
Retrospective analysis of the medical records of 446 consecutive patients with TMC. All patients were treated in one oncology centre between 2012 and 2021 with total thyroidectomy and were in low risk of recurrence group according to ATA stratification system (LR-ATA). During first assessment after the surgery ultrasound examination, stimulated thyroglobulin level, thyroglobulin antybody level and WBS were performed in all patients. Usefulness of WBS in planning further treatment was assessed.
Results
In all 446(100%) patients the radioiodine uptake in WBS was detected only in the thyroid bed. There was no pathological radioiodine uptake in any patients
Conclusion
Routine 131I WBS is not required for patients with LR-ATA TMC after total thyroidectomy. WBS does not affect further management.

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EP632

The Thyroid extranodal marginal zone B-cell lymphoma of MALT: about 2 cases

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Introduction
Primary thyroid non-Hodgkin's lymphoma (PT-NHL), is a quite rare entity, accounting for 1.3–1.5% of thyroid neoplasm, and 0.5% of lymphoma. The extranodal marginal zone B-cell lymphoma of MALT, occurs in 23% of PTL. The aim of our work is to evaluate the clinicopathological features and treatment outcomes of patients with MALT primary thyroid lymphoma. We report two cases of MALT PTL taken care of in our department.
Observation 1
It was 56 years old man, with a history of hypothyroidism. Hospitalized in our department for management of an anterior basicervical swelling evolving for 4 years and rapidly increased associated with a recent deterioration in general condition as well as significant unquantified weight loss and intermittent dyspnea. The physical examination found a hard anterior basic cervical tumefaction, making 5 cm of MA associated with right jugular carotid adenopathy. Cervical ultrasound showed a multinodular goiter. Thyroid fine needle aspiration revealed a cluster of inflammatory cells with plasma cells without signs of malignancy. A lymph node biopsy found malignant cells in small clumps. The patient had a total thyroidectomy. The extemporaneous examination concluded a benign isthmic nodule. The definitive anatomopathological examination showed an aspect of low-grade MALT lymphoma rich in plasma cells. The patient was referred to hematology for additional treatment (chemotherapy). There was no relapse after 4 years of follow-up.
Observation 2
It was, 52 years old woman, with a medical history of adenocarcinoma of the colon in 2011 and neoplasia of the right breast in 2020, both treated by surgery and chemotherapy, who referred to our service for an anterior basicervical swelling evolving for 6 months rapidly increasing in size. The physical examination found a hard anterior basic cervical tumefaction, making 3 cm of MA associated with bilateral jugular carotid adenopathy. Cervical ultrasound showed a multinodular goiter. The patient had a total thyroidectomy. The extemporaneous examination concluded a benign nodule. The definitive anatomopathological examination showed an aspect of low-grade MALT lymphoma rich in plasma cells. The patient had a pet scan which was without abnormalities. Bone marrow biopsy showed non-infiltrated marrow. The hematologists decides then to monitor the patient and not administer chemotherapy because of the different arguments related to the patient and her tumor. There was no relapse after one year of follow-up.
Conclusion
Thyroid (MALT) is 23% of all thyroid lymphomas. The overall survival is estimated to be more than 90%. Its care is multidisciplinary.

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EP633

Carcinological factors associated with adrenal metastases in bronchopulmonary cancer: a comparative study

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Objective
To study the carcinological factors associated with adrenal metastases (AMT) in bronchopulmonary cancer (PBC).
Patients and Methods
Case–control study analysing oncological data of 40 patients with PBC monitored by 18DFG PET/CT at the Nuclear Medicine Centre of Sfax, Tunisia. We compare the characteristics of 2 subgroups:
G1 ($n=17$): patients with PBC and META (cases)
G2 ($n=23$): patients with PBC without META (controls)
Results
The two groups were matched for age and gender. METAs were more common in patients with small cell carcinomas (G1: 17.6% versus G2: 0%; $P=$NS). A small, non-significant frequency of sarcomatoid carcinomas was observed in G1 (G1: 28.6% versus G2: 5.3%; $P=$NS). SUVmax (G1: 15.8±7.8 versus G2: 12.3±7)

and metabolic volume (G1: 35.6 ± 29.5 versus G2: 32.2 ± 4.8 cm^3) of PBC did not appear to influence its metastatic tropism to the adrenal glands.
According to logistic regression, the predictive factors for META were PBC size > 6 cm (OR = 0.063; CI95% = [0.012–0.33]; $P = 0.001$) and the number of pre-existing secondary sites (OR = 5.23; CI95% = [1.85–14.78]; $P = 0.002$).
Discussion
PBC is a neoplasm with a high metastatic potential, particularly in the adrenal glands. 18FDG PET/CT has become the gold standard for the initial assessment and monitoring of PBC. Adrenal involvement should be systematically investigated in the initial staging of PBC, particularly if it is larger than 6 cm and if another secondary location has already been established.

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EP634

Vascular damage after craniopharyngioma – a literature review

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Craniopharyngiomas are rare, embryonic, malformational tumors of the (supra-)sellar region. Due to tumor and/or treatment-related hypothalamic lesions, patients develop morbid obesity. As a major vascular risk factor, obesity leads to reduced 20-year overall survival and a 3- to 19-fold higher cardiovascular mortality after craniopharyngioma compared to the general population. This review studies craniopharyngioma-specific risk factors for vascular damages. Three databases (Pubmed, CINAHL and Web of Science) were searched and 49 articles were included after title and abstract screening. Eligible studies were case reports, cohort and cross-sectional studies. Neurovascular damages due to surgical interventions included cerebral infarcts, stroke, aneurysms, anterior/-middle cerebral artery syndrome (ACA/MCA), cerebral venous sinus thrombosis, and seizures. Radiation-induced vascular disease described Moyamoya syndrome, radionecrosis and thrombosis. Tumor-induced inflammation is suspected to play a causal role in the etiology of vascular complications in proximity of the tumor. Therefore, early diagnostics such as echocardiography or cardial MRI and risk-adapted prevention and treatment options for vascular disease are needed to improve long-term prognosis after craniopharyngioma treatment. This review summarizes the available evidence for vascular disease after pediatric- and adult-onset craniopharyngioma to derive possible treatment pathways. Individualized, tertiary prevention programs are required for craniopharyngioma patients and survivors to overcome or reduce the risk of vascular complications and elevate their quality of survival.

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EP635

Multiple endocrine neoplasia type 1: a case report

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Introduction
Multiple endocrine neoplasia type 1 (MEN1) is a rare, heritable syndrome characterized by a hyperparathyroidism, pituitary adenoma and pancreatic islet cells.
Case
A 56-year-old male patient had a single parathyroid excised for primary hyperparathyroidism 10 years ago. He was further investigated due to hypoglycemia and a mass was found in the head of the pancreas on MRI. It was reported as neuroendocrine tumor and no recurrence was found in the 7-year follow-up. The patient who applied to our hospital for further examination in 2020 has been having intermittent diarrhea attacks for 3 years. In the CT examination, hemangioma in the liver, well-circumscribed tumor in the pancreatic head, and right adrenal nodule were detected. Considering a neuroendocrine tumor, Ga-68 PET/CT examination was performed. High GaTaTe uptakes were detected in the head of the pancreas and in the second part of the duodenum. In addition, nodular thickening was detected in the right adrenal gland, but GaTaTe uptake was not observed. Metanephrine and normetanephrine were examined and found to be normal. PTH: 165.1 (15–65) pg/ml Ca: 11.39 (8.6–10) mg/dl and other tests including pituitary hormone panel, insulin, c-peptide and gastrin were found to be normal. Nephrolithiasis was detected in the CT scans of the patient. There are ulcers in the small intestine on gastroscopy. No adenoma was detected in the pituitary MRI examination. Later, the patient was referred to general surgery for excision. The remaining parathyroid glands were excised. The pancreatic head tumor was found to be compatible with insulinoma, and involvement in the duodenum was found to be compatible with gastrinoma.
Conclusion
The clinical diagnosis of MEN1 is based on the formation of two or more primary MEN1-related tumors (parathyroid gland, anterior pituitary, and enteropancreatic). Our patient is a classic example of MEN1 syndrome with tumors in 2 defining endocrine organs.
Key words
MEN1, Hyperparathyroidism, pancreatic islet tumor.

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EP636

MiNEN of the proximal colon – a strange case

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Introduction
Ectopic ACTH syndromes account for 5–10% of Cushing syndrome, with intrathoracic and gastrointestinal–pancreatic neuroendocrine tumors being the most common causes, followed by small cell lung cancer, adrenal paraganglioma and medullary thyroid carcinoma.
Case report
A 50-year-old male hypertensive and diabetic patient was transferred to our clinic for emergency endocrine care for hypokalemia. He had mild hypercortisolism and liver metastases. We admitted a patient with normal body mass, facial and thoracic hyperemia, lower muscle weakness and a right hypochondriac sensitive normal volume abdomen, without muscular defense signs or stretch marks. Biochemistry tests revealed hypokalemia ranging between 2.5 and 3.7 mEq/l, despite the intensive treatment with potassium chloride and spironolactone, and mild hepatic cytolysis. Hormonal tests confirmed ACTH-dependent hypercortisolism (ACTH > 2000 pg/ml, cortisol > 63.4 mg/dl) and high NET markers-chromogranin A > 900 ng/ml, neuron-specific enolase > 200 µg/l, and CEA (59.18 ng/ml). The CT scan showed hyperplasia of the adrenal glands, a solid nodule of the uncinate process and multiple hepatic tumors suggesting metastases. Ketoconazole failed to control hypercortisolism due to hepatic side effects. The patient was referred for bilateral adrenalectomy, performed in association with right hemicolectomy and ileo-transversal anastomosis, with a slightly favorable evolution afterwards, on gluco and mineralocorticoid replacement therapy with improvement of the ionogram, blood pressure and glycaemia. The histopathological exam confirmed proximal colon carcinoma-ulcerated adenocarcinoma, mucinous component (~35–40%) and large cell neuroendocrine carcinoma (~35%) suggesting a MiNEN (mixed NET and non-NET). The immunohistochemistry (IHC) exam showed positive staining for synaptophysin and chromogranin A, MMR protein (MSH2, MSH6, MLH1, PMS2), intense positive diffuse p53, CK20 and SATB2, a ki67 of 80–85%, but negative staining for ACTH.
Particularities
Despite the negative staining for ACTH, Cushing's syndrome symptoms improved after tumor resection and adrenalectomy. A large tumor may harbor different ACTH expression in different areas, which can be the cause of ACTH negative IHC sample. The age at diagnosis was lower than the known mean age (60 years) and the symptoms onset and evolution were fulminant in this case, almost one month, despite all medical intervention.
Conclusion
Management of ectopic ACTH syndrome due to neuroendocrine tumor is complex. The gold standard is the complete surgical resection of the primary tumor. If the surgery fails, it is important to control hypercortisolemia and prevent its complications. The severity and histological pattern of the tumor is related with the ectopic ACTH syndrome prognosis.

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EP637

Neuroendocrine carcinoma of the vagina in a young patient – a rare entity

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Primary vaginal malignancy is uncommon, accounting for about 2% of all gynecological tract cancers, with small-cell neuroendocrine carcinoma of the vagina being exceptionally rare and aggressive. They display similar histological and immunohistochemical features to small-cell carcinomas of different origin. Few cases are reported in the literature so far and therefore, there is no current treatment protocol consensus. We report the case of a 34-year-old nulliparous patient, who presented for evaluation in May 2022 after palpatory detection of a vaginal mass during ovule treatment, following an annual Pap smear, that showed nonspecific inflammation and was negative for squamous intraepithelial lesion. She was otherwise asymptomatic and had a medical history of two surgically removed polypoid uterine adenomyomas. Family history was also positive for genital and gastrointestinal malignancy. Upon gynecological examination, a highly vascularized, friable, 5 cm mass was identified, located on the posterior vaginal wall, occupying almost the entire vagina. The histopathological biopsy report showed a poorly differentiated carcinoma and immunohistochemistry confirmed a neuroendocrine carcinoma, with SSTR2 expression. The following imagistic screening revealed secondary pulmonary determinations and metastatic adenopathies, and also a solid 6 cm mass on the left ovary. PET-CT scan also showed some metabolically active bone lesion, one on the tenth costal arch. The multidisciplinary team decided initiation of cisplatin and etoposide combination chemotherapy. After 8 cycles, the patient had a good response to the treatment, with normalization of tumoral markers (initially high CA125, CA15-3, CEA) and dimensional regression of the primary tumor, some metastases and of the ovarian tumor. The patient underwent whole-body octreotide scintigraphy with SPECT/CT and is currently being evaluated for surgical excision and radiotherapy of bone determinations. In conclusion, we present the unique case of advanced, metastatic neuroendocrine carcinoma of the vagina in a young patient with associated genital malignancy family history, emphasizing the necessity of a multidisciplinary approach, genetic screening and further study of the disease. Small-cell neuroendocrine carcinoma of the vagina is extremely rare, with aggressive behavior and poor prognosis. Histological recognition of this separate entity is important and multimodality treatment could improve patient outcomes.

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EP638

Multiple endocrine neoplasia: about 9 cases

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Introduction
Multiple endocrine neoplasia (MEN) is a group of inherited syndromes of autosomal dominant transmission characterized by the development of endocrine tumors.
Materials and methods
It is a retrospective study collecting data of 9 patients with MEN, during a 30-year period.
Results
The mean age at diagnosis was 34.6 years with a clear female predominance. The majority of our patients were from Gabes (4 cases). Seven patients had MEN1. The different pathologies described in MEN1 were: primary hyperparathyroidism (PHP/100%), macroprolactinoma and multi-nodular goiter(57%), adrenal adenoma(42.8%) and insulinoma(14.2%). The genetic study was done for all patients except one who died. It revealed the presence of a mutation in the gene coding for Menin in three cases. A new missense mutation at exon-4 of the MEN1 gene, not previously described in literature, was found in our series. Two patients had MEN2. In MEN2A (1 case), PHP was the revealing condition followed by medullary thyroid carcinoma (MTC) and then pheochromocytoma. In MEN2B (1 case), pheochromocytoma was the initial manifestation followed by MTC. Molecular study of the RET gene carried out in both patients (result in progress for MEN2A) showed a mutation in exon-16 (codon,M918T).
Discussion/conclusion
The diagnosis of MEN can be made on a range of clinical arguments but molecular study remains essential to confirm the diagnosis and to give appropriate genetic counselling. The risk of recurrence is high (50% for the offspring of an affected individual). The genetic study also makes it possible to indicate surveillance and early management of asymptomatic family cases carrying the mutation.

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EP639

Neuroendocrine tumors of the head and neck: our experience

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Introduction
Neuroendocrine tumors of head and neck region are rare and heterogeneous. it can arise in all the different organs of this region, including the nasal cavity, paranasal sinuses,, larynx,,thyroid, can be divided into two broad groups: those with epithelial differentiation, and neurally derived tumours, including paragangliomas and olfactory neuroblastomas. Their morphological and clinical features mainly depend on the degree of differentiation and on the site of origin.
Method
A retrospective study was conducted on 37 patients identified with neuroendocrine tumors of the head and neck over a period of 32 years, from 1990 to 2022. Presentation, Clinical examination, evaluation, medical and surgical treatments, histological examination were reviewed.
Results
The average age was 44 years ranging from 11 to 83 years with a sex ratio of 1.2. The average consultation delay was 8 months. We identified 12 patient with paraganglioma and as chief complaint of neck mass, Olfactory neuroblastoma in 7 cases presented with epistaxis and nasal obstruction, neuroendocrine tumors arising from the larynx in 5 cases, consulted for dysphonia and dysphagia, medullary thyroid carcinoma in 12 cases and neuroendocrine carcinoma of the thyroid in 1 case presented for cervical swelling. Treatment courses varied across patients and included combinations of surgery, and/or radiotherapy. Average follow-up time was 2 years. 6 Patients were lost to follow-up. 2 had evidence of known metastases to various sites including bone, and brain. A tumor recurrence was noted in 5 cases.
Conclusion
Neuroendocrine tumors are a heterogeneous group of neoplastic proliferations showing different morphological features, clinical presentation, and treatment outcomes.

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EP640

Parathyroid cancer and of primary hyperparathyroidism

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Parathyroid cancer is a rare cause of primary hyperparathyroidism (PPH). The objective of this work is to discuss clinical and therapeutic specificities of these tumors.
Case n°1
51-year-old woman from a consanguineous marriage, with a family history of recurrent renal lithiasis, neoplasia, and a personal history of breast neoplasia and uterine fibroid, consulted for abdominal pain, vomiting and weight loss. The diagnosis of primary hyperparathyroidism was made in view of hypercalcemia (3.65 mmol/l), hypophosphatemia (0.62 mmol/l), PTH = 2701 pg/ml (41*N), hypovitaminosis D < 8 ng/ml, Clcreatinine = 86 ml/min. A left retro-thyroid nodule and 2 right sub-thyroid nodules on cervical ultrasound were noted. The Technetium-99m-sestamibi scan showed a left retro-thyroidal mass 21 × 16 × 37 mm and a right inferior latero-tracheal nodule 13 × 16 mm fixing MIBI. Hyperparathyroidism-jaw tumor-syndrome was strongly suspected; mandibular radiography didn't show any ossified fibroids. The

search for HRPT2 gene mutation is in progress. A left lobo-isthmectomy with homolateral mediastino-recurrential evacuation and a right and left upper parathyroidectomy were performed. anatomopathology examination revealed a 5 cm left upper parathyroid carcinoma with oxyphilic cells and 2 atypical parathyroid nodules of the right upper pole of 1.5 cm.
Case n°2
Sporadic PPH complicated by recurrent lithiasis and osteoporosis in a 68 year old man secondary to a necrotic cervical-mediastinal ectopic right lower parathyroid mass. Malignancy was suspected due to the large size (8 cm), and a PTH of 16 times normal. The patient underwent carcinological surgery and total thyroidectomy for a multinodular goiter. Anatomopathology examination is in progress
Case n°3
57-year-old patient, with a personal history of hypertension and primary infertility, consulted for incoercible vomiting, asthenia and fever.The bilogy: hypokalemia (2.7×mmol/l), renal insufficiency (clcréat = 29 ml/min), hypophosphoremia (0.45 mmol/l), hypercalcemia (4.02 mmol/l) with electrical signs (QT shortening) requiring an emergency hemodialysis session. Primary hyperparathyroidism was diagnosed with a PTH = 570 pg/ml (8.7*N), a plunging cystic mass with some parietal calcifications, measuring 40×56×90 mm and largely necrotic, not fixing MIBI. The evolution was marked by the appearance of epileptic seizures, followed by an alteration of his state of consciousness in relation to a Wernicke's encephalopathy on MRI.

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EP641

Cervical paragangliomas: clinical presentation and Managment modalities

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Introduction
Paragangliomas are a diverse group of neuroendocrine tumors arising from chromaffin cells within paraganglionic tissues of the autonomic nervous system. The aim of this study is to review our experience in the management of these tumors.
Methods
The medical records of 12 patients with 13 paraganliomas was performed in a a single academic hospital over a period of 32 years from 1990 to 2022.
Results
There were 10 women (83.3%) and 2 men (16.6%) with a mean age of 47 years. A painless lateral neck mass was the main finding in 10 cases. There was no evidence of a functional tumor. Computed tomography was performed in 8 cases and MRI in 11 cases.The majority of the lesions were paragangliomas of the carotid bifurcation (7 cases), while 5 patients with a vagal paraganglioma. Bilateral vagal paragangliomas were detected in one case. Secretory activity was studied in 6 patients. All patients had normal level of metanephrines. For patients treated with radiotherapy, Radiotherapy was able to control growth in all treated tumors. 8 patients treated surgically. The most commonly affected structures were the facial nerve, the vagus nerve and the hypoglossal nerve and Sympathetic chain palsy as a sequela of the surgery. Average follow-up time was 36 monthes and there were no regional recurrence.
Conclusion
Surgery and radiation therapy represent the main treatment modalities for paraganglioma. Although surgical resection has remained the mainstay of treatment for paragangliomas, the need for preoperative embolization remains controversial. Secretory and malignant tumors are extremely rare and requires active management.

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EP642

Syndrome of inappropriate antidiuretic hormone secretion associated with olfactory neuroblastoma

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Introduction
Olfactory neuroblastoma causing syndrome of inappropriate antidiuretic hormone (SIADH) as paraneoplastic syndrome is very rare. There have been only 10 cases with antidiuretic hormone (ADH) producing olfactory neuroblastoma in the literature. The syndrome is due to ectopic production of protein hormones, hormone precursors, or hormone-like substances by the tumor tissue. Here, we report the case of olfactory neuroblastoma associated with SIADH.
Observation
Patient S.D., 25 years old, with a history of inappropriate ADH secretion syndrome (SIADH) under NaCl, had consulted for unilateral left nasal obstruction evolving for five months. Examination revealed a fleshy, richly vascularized tumor mass filling the entire left nasal cavity. The right nasal cavity and the cavum were free. A biopsy was performed and the diagnosis was an inverted papilloma. The CT scan of the facial mass revealed a 23×41 mm hyperdense nasosinusal tumor formation with blowing calcifications extending to the maxillary sinus and to the homolateral ethmoidal cells coming in contact with the papyraceous lamina and the roof of the ethmoid. MRI of the facial mass showed a left maxillary tissue process of 40×25×45 mm. The walls of the left maxillary sinus are thinned but continuous. Retentional filling of the maxillary and left frontal sinuses and no brain abnormalities. The patient underwent a middle meatotomy, anterior and posterior ethmoidectomy and left sphenoidotomy by endonasal approach removing the tumor. The immediate postoperative course was simple. The extemporaneous examination was in favor of a massive tumor, non vascular, without histological signs of malignancy. The final anatomopathological examination concluded to an olfactory aesthesioneuroblastoma stage II of Hyams. The patient was proposed for postoperative RT, but the patient did not reconsult.

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EP643

atypical revelation of anaplastic thyroid cancer

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The aim of this study is to report a case of an unusual presentation of anaplastic thyroid carcinoma and describe its clinical, radiological and management particularities. Observation: We report the case of a 60 year-old female patient who presented with a two-week history of progressive aphagia, associated with hemoptysis. She also described recent shortness of breath, and a painless cervical mass evolving for 10 months, rapidly enlarging during the last four weeks. Her medical history was uneventful. Physical examination found bilateral fixed hard masses of the cervical sectors II and III, measuring 5 cm on the left, and 10 cm on the right with an extension to sector III. Nasofibroscopy revealed a suspect left subtonsillar mass, hiding the hypopharyngeal and laryngeal structures. Its biopsy showed unspecific necrotic tissues. CT scan objected a hypopharyngeal mass, measuring 102×78×62 mm, extending inferiorly to the larynx, posteriorly to the prevertebral space, invading anteriorly the right thyroid lobe and reaching laterally the subcutaneous tissues. Multiple cervical necrotic lymph nodes and thrombosis of the right internal jugular vein were associated. On thoracic images, pulmonary metastases were found. Due to aggravation of her dyspnea, the patient underwent tracheotomy, during which a second biopsy was done. Anatomopathological study with immunohistochemistry (PAX8, cytokeratin and TTF1) discovered an anaplastic thyroid carcinoma. Palliative radio and chemotherapy were indicated, but the patient was lost of sight. Conclusion: Considering the rapidly lethal potential of anaplastic thyroid carcinomas, it is important to have in mind this entity as a differential diagnosis for head and neck tumors.

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EP644

Mixed papillary–medullary thyroid carcinoma and cystic adrenal mass

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Introduction
Regardless of the fact that the incidence of thyroid cancer has increased significantly in recent years, the simultaneous occurrence of multiple tumors in

one thyroid gland is still a rare phenomenon. These tumors have the morphology, either of a single mass with mixed histological features, or of a single lesion consisting of two distinct cell-populations, or of two different tumors between which normal thyroid tissue is interposed. Various theories have been proposed as causes for the co-existence of papillary and medullary thyroid carcinoma, however the exact mechanism remains unclear.
CASE REPORT
A 42-year-old man referred to our department, for thyroid ultrasound evaluation, that had shown two large nodules in the right lobe (3×2.29 cm, TIRADS-4 and 4.6×2.01 cm, TIRADS-3). Laboratory evaluation showed normal thyroid function, but high calcitonin values 108.9 ng/ml(<14), which raised a strong suspicion of medullary carcinoma. The patient was advised that the best therapeutic approach was surgery, after performing laboratory and imaging tests related to Multiple- Endocrine-Neoplasia-syndromes (MEN). Free 24-hour urinary metanephrines, as well as other indicators of endocrine neoplasms were within normal limits. However, adbominal Computed-Tomography(CT) revealed a mass 2 cm in the left adrenal gland, with increased Hounsfield-units(HU) and absolute-late-washout>50. An additional Magnetic-resonance-imaging(MRI) was deemed necessary, which, due to the SARS-COV-2 pandemic, was not performed immediately. The patient underwent total thyroidectomy, and histology examination revealed mixed thyroid carcinoma with papillary (80%) and medullary (20%) components. Immunohistochemistry was positive for BRAFV600E mutant protein in all neoplastic cells. The patient was treated with ^{131}I administration, and Whole-Body-Scan(WBS) showed no abnormal findings. Thyroglobulin values with TSH>100 was undetectable, while calcitonin and CEA at 6 and 12 months postoperatively were within normal limits. An abdominal MRI was performed, which did not rule out cystic pheochromocytoma. However, that was not confirmed by the other laboratory and imaging tests(MIBG), nor by clinical symptoms.
Conclusion
Measurement of calcitonin during initial thyroid nodule workup, is helpful in detecting medullary carcinoma. Mixed-medullary-follicular-thyroid-carcinoma(MMFCC) is an extremely rare form of thyroid malignancy and prognostically, the behavior is usually analogous to medullary component. The therapeutic approach is based on the partial treatment of each neoplasm separately. Cystic pheochromocytomas have atypical imaging and clinical features, while symptoms from catecholamine hypersecretion is proportional to the size of the solid part, so these are often silent. In the coexistence of medullary thyroid carcinoma and cystic adrenal lesions, testing for pheochromocytoma is necessary.

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EP645

Tall cell variant of papillary carcinoma on ectopic thyroid tissue

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Introduction
Ectopic thyroid tissue is a rare developmental abnormality due to aberrant embryogenesis and/or migration of the thyroid gland. Although rare (<1%), papillary thyroid carcinoma is the most common malignant transformation.
Aim
Report a case of Tall cell variant of papillary carcinoma occurring on ectopic thyroid tissue in the thyroglossal duct.
Observation
A 56-year-old male patient consulted for a cervical mass appearing two years before, with progressive dysphonia. On physical examination, the patient had a firm tumefaction in the anterior cervical region, with undetermined limits, measuring approximately 7 cm. The thyroid gland was in the normal position. The thyroid function was normal. Neck ultrasound showed a heterogeneous hyperechoic left paramedian cervical mass with much vascularization on Doppler examination. No focal lesion in the thyroid gland was revealed. Cervical MRI provided a more precise assessment of the extension of the mass and confirmed the integrity of the other structures. The tumor was totally resected via a cervical approach. Histological examination confirmed its thyroidal nature, with the presence of tall cell variant of papillary carcinoma without capsular or vascular embolism. The treatment was completed by a total thyroidectomy and bilateral central lymph node dissection. The histological results were normal. The patient underwent radio-iodine therapy, 6 months after the surgery, with elevated initial thyroglobulin at 60 ng/ml. Later on, he developed lung and pleural metastases refractory to iodine. Thyroid suppression therapy was prescribed as an adjuvant treatment.
Conclusions
Although rare, papillary carcinoma on ectopic thyroid should be evoked before any mass of the hyoidal region. Its diagnosis is histological, only after surgical excision of the lesion. The treatment is primarily surgical associated with radioiodine I-131 therapy and suppressive hormone replacement therapy.

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Multiple Neuroendocrine tumours and role of clinical screening versus genetic testing

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Neuroendocrine neoplasms (NENs) are rare but diverse group of malignancies that can arise from gastroenteropancreatic tract and lungs. NENs can be clinically symptomatic (functioning) or silent (non-functioning). We present a case found to have multiple NENs in the absence of known clinical syndrome and discuss role of genetic testing versus clinical screening. 54 Female, referred to endocrine team for investigation of hypoglycaemic symptoms and suspected insulinoma. Routine biochemistry and 0900 h cortisol was normal. 72 h fasting revealed severe hypoglycaemia (blood glucose of 2 mmol/l) with inappropriately normal insulin levels. No Past medical history or family history. No clinical features of VHL syndrome, Neurofibromatosis and Tuberous sclerosis. Other Fasting gut hormones, 24-hour urinary 5HIAA was all normal. CT scan of Abdomen Pelvis showed 1.3 cm arterial enhancing lesion in body of pancreas and a lesion in terminal ileum with mesenteric lymph nodes involvement. Colonoscopy showed Random terminal ileum biopsy showed inflammation only. Octreotide scan revealed positive uptake in ileocecal lesion and adjacent nodes. No uptake in pancreas. EUS showed 1.1 cm hypo echoic lesion in body of pancreas, 2 cm distal to confluence area. MEN 1 screen (Calcium, PTH, pituitary profile) and MEN 2 screen was negative. plasma metanephrine and normetanephrine were normal. After discussion in GIT MDT, Distal pancreatectomy and ileocecal resection for 2× NENs was done. Histopathology showed Well differentiated NEN terminal ileum Ki67 1%, G1, 9 out of18 lymph nodes involved. T4, N1 R0. And Well differentiated NEN pancreas, Grade 1, pT1 Nx R0. Histology revealed insulin positive staining in keeping with insulinoma, proliferation index Ki67 < 1%. Patient had uneventful surgery but developed post operative collection managed successfully with surgical drain and antibiotics. Patient had dietician and MDT input clinically improved and discharged with endocrine team follow-up.
Discussion
We are aware that rare genetic mutations can lead to multiple NENs include MEN 1, MEN 2, NF1, VHL, TSC1 and TSC2. Clinical screen for these syndromes should be done in such patients to help us decide surveillance and follow-up. Suspected patients should be tested for these genetic mutations. Although there are no guidelines or studies to suggest whether doing genetic testing, in the absence of negative clinical screen, would be of any additional benefit. We will discuss role of each in details. Further studies are needed to see if there are other genes that can play role in development of multiple NETs.

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Recurrent insulinoma: Case report

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Background
Insulinoma is a rare neuroendocrine tumor that causes inappropriate secretion of insulin resulting in hypoglycemia. The diagnosis of insulinoma may be difficult. Recurrence after surgery is rare and it usually concerns tumors with high histological grade.
Case presentation
We report a case of a 52-year-old woman with recurrent episodes of symptomatic hypoglycemia. The laboratory investigations showed high insulin (20 IU/ml) and C-peptide levels (5.02 ng/ml) concomitant with low blood sugar levels (38 mg/dl) and absence of plasma sulfonylurea. Preoperative pancreatic imaging was negative. Exploratory surgery was performed and the peroperative ultrasound showed a pancreatic tumor of 1 centimeter. Enucleation of the tumor was performed and histopathology confirmed the diagnosis of a grade 1 insulinoma (Ki 67 <1%). Ten years later, she started experiencing symptomatic episodes of hypoglycemia with inappropriately elevated insulin (16 IU/ml) and C-peptide levels (3.03 ng/ml). Pancreatic MRI showed an 11×16 mm tumor. Splenectomy was performed and

histology confirmed the diagnosis of insulinoma. Workup for multiple endocrine neoplasia turned out to be negative.
Conclusion
Insulinoma is a rare tumor that may be life-threatening by causing severe hypoglycemia. Although recurrence of sporadic insulinoma is rare, a clinical follow-up is necessary after surgery.
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EP648

Insulinoma in elderly
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Introduction
The insulinoma is a rare neuroendocrine tumor derived from the beta islet cell of the pancreas. It is usually sporadic and benign in 90% of the cases. It occurs more often in women in their fifties.
Observation
We report the case of 76-year-old women with a medical history of hypertension and dyslipidemia, who was transferred to our department from the emergency unit after a diagnosis of severe episode of hypoglycemia (glucose level at 0.2 g/l) with neurologic manifestations resistant to intra venous glucose supplementation. Indeed, these episodes began in the previous six months with symptoms worsening over time. During her hospitalization, the patient presented a spontaneous hypoglycemia with a glucose level at 0.43 g/l, the insulin level was high at 21.6 µUI/ml > 3 µUI/ml and the peptide C level was at 4.10 ng/ml > 0.6 ng/ml in favor of an endogenous hyperinsulinism. The dosage of hypoglycemic sulfonamides was negative. An abdominal MRI was performed showing a 25 mm exophytic and hyper vascularized mass of the pancreas corresponding to an insulinoma. The patient was referred to surgery which was performed with no complications and the histopathological examination of the removed tissue confirmed the diagnosis of a G2 neuroendocrine tumor.
Discussion
Insulinoma is the most frequent neuroendocrine pancreatic tumor. Surgery represents the first line treatment. Others options such us diazoxide and octreotide can be discussed especially if the malignancy is suspected.
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EP649

Asymptomatic Pheochromocytoma in a patient with Adrenal Incidentaloma
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Background
While the classic presentation of pheochromocytoma includes a triad of episodic headaches (90%), diaphoresis (60–70%), and palpitations (70%), literature has suggested 10% to 17% of patients with pheochromocytoma are either asymptomatic or mildly symptomatic; thus, highlighting the importance of appropriate endocrine work up of adrenal incidentalomas.
Case
We report a 37-year-old male with a long-standing history of nocturia and dysuria, who was managed by a urologist for prostatitis. Further evaluations with CT-kidneys, ureters and bladder showed an incidental rounded left 3×2 cm mildly hyper-attenuating adrenal mass, and the patient was referred to Endocrinology clinic for assessment of the adrenal incidentaloma. Other than dysuria and nocturia, no history of headache, diaphoresis, palpitations, or hypertension were of note. There was no family history for pheochromocytoma or paraganglioma. Physical examination was unremarkable including heart rate and blood pressure (24-hour blood pressure monitoring showing an overall average of 124/86 mmHg, with a range of 117/77 to 126/88 mmHg). Adrenal hormone work-up showed elevated plasma normetadrenalin [1.2 nmol/l (reference range < 0.71)] and plasma metadrenalin [5.62 nmol/l (reference range < 0.36)]. A repeat test showed a persistent elevation of both plasma normetadrenalin and metadrenalin at 1.52 nmol/l and 6.52 nmol/l, respectively. Other tests including full blood count, renal, liver and bone profiles, urinalysis, urine culture and sensitivity, FSH, LH, testosterone, post-dexamethasone suppression test cortisol (26 nmol/l), serum aldosterone (143 pg/ml), active renin (5.6 pg/ml), aldosterone:renin ratio (25.54), DHEAS (8.96 µmol/l) and delta androstenedione (4.89 nmol/l) were within normal limits. CT adrenals with contrast demonstrated a left adrenal rounded 3 cm mass with Hounsfield unit 43/84/60 and absolute washout calculation 60% and relative washout 28%, which is not consistent with adenoma. Echocardiogram showed no significant abnormality thus out-ruling catecholamine associated cardiomyopathy and an MIBG scan was also indicative of a solitary left sided pheochromocytoma. Following a course of alpha blockade with doxazocin, the patient underwent laparoscopic resection of the left adrenal mass and it was confirmed to be pheochromocytoma histologically. At post-surgery the patient remained well and repeat plasma metanephrine levels were within normal limits and required no long-term medications. Genetic tests results concluded no genetic abnormality was detected.
Conclusion
Our case demonstrated that a patient may not have classical symptoms of pheochromocytoma but could have significantly elevated plasma metanephrine levels. Our case also highlights the importance of an urgent assessment of adrenal masses in people <40 years of age as recommended by European Society of Endocrinology clinical practice guideline on adrenal incidentalomas.
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Hidden insulinoma overlapped with pregnancy – a challenge for the clinician
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Introduction
Insulinomas are the most common cause of hypoglycemia due to endogenous hyperinsulinism. Almost all insulinomas are benign, and long-term recovery with complete disappearance of preoperative symptoms can be expected after complete resection.
Case report
A 33-year-old woman, who developed gestational diabetes during her second pregnancy, which persisted post-partum, stopped insulin due to recurrent severe hypoglycemia, but which persisted even after stopping insulin, which is why she presented in our department where the suspicion of insulinoma was raised because plasma glucose was 27 mg/dl, concomitant to a high insulinemia of 50.1 µIU/ml. The imaging investigations were normal. Nuclear imaging investigations were also normal. In dynamics, plasma glucose values remained low (13 mg/dl) and insulinemia increased (169.8 µIU/ml), which motivates the initiation of somatostatin analog (SSA). However, the hypoglycemic status was maintained, so the dose of SSA was increased. Although there was no clear imaging localization following the high suspicion of insulinoma it was decided to perform distal pancreatectomy. Post-operative, the patient's condition was good, so the somatostatin analog was stopped. At 8 months follow-up after the surgery, the patient had a normal plasma glucose level and a normal insulinemia level but later hypoglycemic episodes appeared again, which was why the administration of the SSA was restarted but the patient voluntarily stopped the treatment. At the next follow-up, the pregnant patient at that time presented with increasing insulinemia, thus deciding to continue the treatment with SSA with the patient's consent, although there are relative contraindications for administration during pregnancy. The patient was monitored throughout the pregnancy, hypoglycemia prophylaxis was performed but the fetus was small for gestational age (SGA) according to ultrasound evaluations. Due to an obstetrical complication, premature induction of labor was performed at 28 weeks of pregnancy. Post-partum, the patient's status was reevaluated, the imaging and nuclear investigations results showing no pathological images. During the last visit it was decided to increase the frequency of administration of the SSA.
Conclusion
The SGA new-born can be explained both by the mother's persistent hypoglycemic status and by the administration of the SSA which has been proven to lead to intrauterine growth restriction. With a continuous persistence of hypoglycemia despite the distal pancreatectomy, although without imaging evidence of the localization of the insulinoma, the final step of treatment would be cephalic pancreatectomy, a difficult surgery, with multiple complications and with the need for post-operative replacement of the pancreatic exocrine and endocrine function.
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Acromegaly and papillary thyroid carcinoma: Incidental association or causal link?

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Introduction
Acromegaly is an unusual endocrinopathy due to hypersecretion of growth hormone (GH) and concomitant rise of IGF-1. It is associated with premature of mortality caused by cardiovascular, respiratory and metabolic diseases, as well as increased risk of developing boh benign and malignant tumours. We report the case of a patient with acromegaly associated with papillary thyroid microcarcinoma (PTC).
CASE
A 50-years -old male patient, followed for acromegaly for 2 years, underwent subtotal transphenoidal surgery of the pituitary macroadenoma with surgical failure as shown on the follow-up hypothalamic–pituitary MRI. As part of the workup, a cervical ultrasound was performed, which showed a multiheteronodular goiter for which he underwent a total thyroidectomy. The anatomopathological examination was in favor of a papillary thyroid microcarcinoma.
Discussion ans conclusion
The coexistence of acromegaly and thyroid cancer is rare. The recrudescence of these two tumors can be explained by the fact that both GH and IGF-1 have mitogenic and anti-apoptotic properties. In addition, as both normal and malignant thyroid cells express IGF-1 receptors, an autocrine role for IGF-1 has been demonstrated in human thyroid cancer cell line. The risk of developing thyroid nodules increases with the age of the disease, hence the interest of regular surveillance because of the risk of malignancy.

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Different phenotype of familial RET mutation in 2 patients: Medullary thyroid carcinoma and Adrenal Paraganglioma

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Introduction
RET proto-oncogene is situated on chromosome 10 and encodes a tyrosine kinase receptor. A germline mutation of RET leads to the appearance of MEN 2 syndrome or familial medullary thyroid carcinoma (MTC). One of the most common germline mutation occurs in codon 634. Pheochromocytoma penetrance for codon 634 mutation was demonstrated to increase with age up to 88% by age 77 years.
Aim
To present two familial cases of RET mutation illustrating the different phenotypes that can arise.
Case 1: 44 years old woman who came in our clinic with bilateral hypoechoic thyroid nodules, elevated calcitonin and a slightly raised parathyroid hormone (PTH) with no symptoms. In our center hormonal assessment reflected: calcitonin = 861 pg/ml (n = 1–11), CEA = 76.09 ng/ml. Blood testing for pheochromocytoma and hyperparathyroidism were within the normal range. Fine needle biopsy was performed and the suspicion of MTC (Bethesda V) was confirmed. RET gene analysis showed heterozygous mutation Cys634Trp in exon 11 of RET gene. The patient underwent total thyroidectomy with bilateral jugulocarotid lymphadenectomy, right upper parathyroidectomy and the diagnosis of MEN 2A was confirmed. We did genetic family screening by evaluating her son (negative for RET mutation) and her father, whose case is detailed below.
Case 2: 73 years old man, with grade II hypertension and chronic gastritis, presented with dizziness, nausea and 5 kg weight loss over 3 months. Computed tomography examination showed right adrenal 16×12 mm nodular formation and a cystic formation of 30×22 mm in the left adrenal gland. Subsequent endocrine evaluation revealed high plasma metanephrines in two consecutive measurements: 237 pg/ml, respectively 291 pg/ml (n = 0–100), high cromoganin A, slightly high plasma normetanephrines and a non-suppressed cortisol level after 1 mg of overnight dexametazone. Results of blood testing for hyperparathyroidism and MTC were within the normal range. After performing RET gene analysis, same mutation was confirmed, which guided us to classify the patient into Cluster 2 Adrenal Paraganglioma. The patient underwent preoperatory preparation with doxazosin for laparoscopic right suprarenalectomy.
Conclusion
Screening first-degree relatives for RET mutation is highly recommended because it helps diagnosing adrenal paraganglioma even at average values of hypertension, as well as advanced ages.

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The occurrence of adrenocorticotropic hormone-independant Cushing's syndrome in a woman with the history of medullary thyroid carcinoma: a case report

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Background
Medullary thyroid carcinoma (MTC) is a rare neuroendocine tumor that that may be associated with paraneoplastic ACTH-dependent cushing syndrome. There are few case reports on the coexistence of medullary thyroid carcinoma and adrenal adenoma with ACTH-independent Cushing syndrome.
Case presentation
We report the case of a 42-year-old woman, with no family history of endocrine malignancy or endocrine disorders. She underwent total thyroidectomy for MTC. During follow-up, she presented with high blood pressure, hypokalemia, diabetes, and osteoporosis. These symptoms led to the suspicion of Cushing's syndrome. The investigations indeed showed an excessive production of cortisol. contrary to what was expected, Cushing's syndrome is of adrenal origin. Abdominal CT scan showed adrenal adenoma.
Conclusions
We present a rare case of a patient with MTC and Cushing's syndrome. The co-occurrence of two endocrine tumors with different origins is rare. To date, no known genetic syndrome can account for this combination of neoplastic thyroid and adrenal pathologies, future research may prove differently.

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Weight loss in diabetics of 2 unbalanced revealing neoplasia

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Introduction
The incidence of cancer has increased in case of diabetes, as well as the metabolic abnormalities observed during diabetes could have a critical role on carcinogen, nevertheless one should not deny the implication of common factors to diabetes and cancer (obesity, smoking, advanced age, etc).
Study objectives
Describe the biological and morphological screening methods for neoplasia in the event of weight loss concomitant with chronic glycemic imbalance.
Materials and methods
Retrospective descriptive study conducted at the endocrinology and metabolic diseases department of Casablanca, including 186 patients hospitalized for chronic glycemic imbalance with weight loss between 2018 and 2022.
Results
A total of 186 patients were included, reporting an average weight loss of 7.6 kg provided a weight loss assessment including an assay of tumor markers (CA19.9, ACE, CA15.3, CA125, PSA) and morphological minimal (thoracic X-ray and pelvic ultrasound), a specific morphological assessment was carried out in the event of an anomaly (echo-mammography, abdominal cervicothoracic computed tomography) or even a cervical–vaginal smear. The average age was 58.3 years with a female predominance, HBA1C averaged 11.7%, obesity was found in 69.2%, sedentary lifestyle in 91%, smoking in 39.6%, and alcoholism in 18.5%. Among them, 16 patients presented neoplasia including 7 pancreatic neoplasia, 5 mammary, 2 cervical–vaginal, 2 pulmonary and 1 case of esophageal neoplasia.

Conclusion
A chronic diabetic imbalance could suggest a neoplastic cause. Early screening for these neoplasia's is important and should include a stratification model with clinical–biological criteria, and specific imaging.

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Recurrent adrenocortical carcinoma: a case report

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Background
Adrenocortical carcinoma is a rare malignancy with a poor prognosis. Local recurrence is affected by the pathologic features (tumor staging and mitotic index) and the complete surgical resection. Treatment of a recurrent adrenocortical carcinoma can be a real challenge.
Case description
We report a case of 47-year-old man who was operated for an adrenal tumor with bone metastases. Left adrenalectomy and splenectomy were performed and histology confirmed the diagnosis of adrenocortical carcinoma. Five cycles of chemotherapy (Cisplatin and bisphophonate) were given. The patient presented an adrenal deficiency and a 10 mg glucocorticoid replacement therapy was prescribed. Seven years later, he presented dyspnea and fatigue with no other clinical or biological abnormalities. CT scan showed a left adrenal tumor of 40× 30 mm and a suspected voluminous lymph node of a 90×63 mm with invasion of the left pulmonary artery and multiple suspected pulmonary lesions. Cortisol failed to suppress after low dose and high dose on Dexamethasone suppression test. Surgery was not possible and the patient continued to deteriorate despite chemotherapy and was subsequently referred to palliative care.
Discussion
Due to the rarity of the adrenocortical carcinoma, the understanding and experience of management modalities is limited. New treatment options may be available in the coming years to improve outcome. Early identification of tumor is the key to improve the prognosis of the disease.

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Primary sinonasal neuroendocrine carcinoma invading the orbit

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Introduction
Sinonasal neuroendocrine carcinoma SNECs are a rare group of neoplasms that account for only 5% of all sinonasal malignancies. SNECs are categorized by their differentiation grade into well-, moderately- and poorly differentiated.
Case report
We describe a classical case of SNEC with secondary orbital involvement in a 34-year-old male patient presented of the occurrence of a right epistaxis. First of all, the patient is smoking. The beginning of the symptomatology goes back to 2 months before with right nasal obstruction of progressive onset, associated with bloody rhinorrhea and right chronic eye watering. The patient didn't present neurological signs nor cervical lymph nods. Otherwise, ophthalmologic examination found normal visual acuity and ocular mobility on both sides. Sinonasal computed tomography (CT) found a right nasal process enhanced after injection of contrast product 46×30×37 mm invading the orbit. The immunohistochemical study of the tumor biopsy found that the pan cytokeratin and CK7 and the neuroendocrine marker Chromogranin A, synaptophysin and CD56 are positive, with a proliferation index Ki67 of 60%. The multidisciplinary decision taken was treatment by chemotherapy before surgery.
Discussion
Most patients present at advanced stages due to the lack of significant symptoms. Advanced tumors may invade the skull, orbit or brain. Ophthalmic manifestations include exophthalmos, reduced vision and restriction in ocular motility. Ectopic hormone secretion has been described in a handful of cases. Staging is of limited value in predicting prognosis and recent literature clearly highlights the importance of histological diagnosis, particularly differentiation grade, in determining the prognosis and predicting treatment response.
There are no clear treatment and the management include surgery with radiotherapy with/without chemotherapy; chemoradiotherapy; or radiotherapy or chemotherapy alone.

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Digestive endocrine tumors: better understanding for better treatment

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Introduction
Digestive neuroendocrine tumors (DNETs) represent a heterogeneous group of tumors. This heterogeneity is manifested by the variable localization of these tumors but also by a great clinical and biological diversity. Thus, they occupy an increasingly important place in digestive oncology.
NETs are very rare and represent about 1% of all digestive tumors, due to their slow evolution. The majority of them develop in the digestive tract (67.5%) (from the esophagus to the anus); the pancreas, the liver and the gallbladder are more exceptionally affected.
We report the observation of a patient with a type 1 neuroendocrine tumor to illustrate the interest of properly typing this type of tumor in order to administer an adequate treatment.
Observation
49 year old patient with antecedents: Biermer's anemia under treatment
Who has chronic intense epigastric pain that is resistant to analgesic treatment and for which endoscopic exploration has demonstrated: Milimetric sessile polyps in the fundus with suspected ECLomas and a histological and immunohistochemical appearance of a well differentiated DNET of grade 2+ Chronic antral gastritis.
The clinical examination was unremarkable.
A workup that could frame TNED as a possible type 1 multiple endocrine neoplasia was requested:
On the biological level:
Gastrinemia 17×N.
Chromogranin A elevated at 172 ng/ml (N: 108 ng/ml).
Insulin, C-peptide, hypophysiogam and Ph-Ca were normal at normal rate.
On the morphological level:
CT scan and Hypothalamic–pitiutary MRI without any particularities
An Otrescan for metastases was requested but did not reveal any other pathological sites
→We conclude to a neuroendocrine tumor type 1
The treatment consisted of clinical surveillance with iterative endoscopic tumorectomy every 6 months.
Conclusion
In the vast majority of cases, differentiating neuroendocrine tumors does not pose a real problem. A few simple rules can help to avoid any diagnostic doubts. The challenge is not to overtreat benign tumors (type 1) and induce surgical morbidity and mortality, or undertreat malignant tumors (type 3).

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Clear cell renal carcinoma synchronous with various endocrine pathologies

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Introduction
Clear cell renal carcinoma (ccRCC) is a subtype of renal cell carcinoma, the most frequent one (80%) and usually affecting only one kidney. It is twice as common in men than women between 50 to 70 years old. It can be associated with some genetic conditions that predispose patients to ccRCC, like Von Hipple-Lindau disease. Some clinical observations and molecular studies raised the hypothesis that RCC is a hormone−dependent tumor.
Case reports
We present three cases of ccRCC associated with various endocrine patterns.
Our first case is a 45-year-old man, with a family history of papillary thyroid carcinoma and ccRCC, left nephrectomy for ccRCC and nontoxic multinodular goiter. One year after nephrectomy, he underwent total thyroidectomy (confirmed

histopathological to be a papillary thyroid carcinoma). The second case is a 46-year-old woman who underwent a partial right nephrectomy and right adrenalectomy. The histopathological exam revealed ccRCC and adrenal metastasis of ccRCC. MRI scan showed left longissimus thoracic muscle nodule and left adrenal nodule suggesting metastasis, while having a normal adrenal function. The patient was referred to initiate immunotherapy, therapy that can lead to thyroid disfunction. Our third case is a 52-year-old woman, known with lupus, without documented lupic nephritis, and left nephrectomy for ccRCC. One year after nephrectomy, the patient contracted left shoulder pain, which led to the diagnosis of left humeral osteolytic metastasis, so she started Sunitinib treatment (4 weeks on, 2 weeks off). Six months later, she developed sever hypothyroidism (TSH = 320 × μUI/ml) and began replacement therapy. All our cases are peculair. Age at diagnosis was lower than the known mean age (64 years). Men are predisposed to develop first thyroid cancer (opposite to our case), then kidney cancer, with a distance between the two cancer diagnoses of 5.2 years. Bilateral adrenal metastases are rare (< 0.5%), particularly in case of melanoma, thyroid, hepatocellular and bladder cancer, not in ccRCC. Hypothyroidism is a side effect of Sunitinib (TKI), in patient with underlying autoimune thyroid condition, or through the inhibition of VEGFR and/or PDGFR.. During the treatment with Sunitinib, the patient may need a higher dose of levothyroxine than during the treatment break.

Conclusion

The risk of developing another primary tumor is three times higher in patients with RCC versus other oncology patients. The gold standard in localized RCC is nephrectomy and local lymphadenectomy. In case of metastatic RCC, some of the treatment options are TKI (sunitinib e.g.) and immunotherapy.

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Environmental Endocrinology

EP659

Are sugar substitutes potential endocrine disruptors?

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Keywords: sugar substitute agent exposures, nutritional biology, neuroendocrine system, oxytocin

Human homeostasis is maintained by the complex functioning of the psycho-neuroendocrine-immune system. If a disturbance is generated in this neuroendocrine system for any reason, it can trigger pathogenic processes. One of the factors disturbing homeostasis today may be changes in dietary habits, e.g. through the use of undue sweeteners (e.g. stevia, xylitol etc.). These substances may alter neuroendocrine regulation if they affect natural metabolic processes. *In the present work we aim* to follow the changes in oxytocin (OT) relase induced by certain sugar substituting agents. Continuing our research on this topic, where we have already explored the effects induced in AVP ablation. *In our work*, we treated Wistar (♂) rats *in vivo* with gastrointestinally sweetening agents (aspartame, stevia, saccharin, xylitol) while monitoring their toxicity parameters. At the end of the treatments, *in vitro* neurohypophysis monolayer cell culture models (NH) were prepared (enzymatic /trypsin, collagenase, dyspase enzymes/ and mechanical /d = 80 μm neylon-blutex filter/ dissociation; DMEM + 10% FCS + 10U/ml Pen + Strep culture medium). These were used to study OT regulation after viability, specific-, aspecific function control. We measured the basal OT release of NH wells from confluent cultures formed after in vivo treatment and also determined OT release in vitro in the presence of additional aspartame, stevia, saccharin, xylitol (1 mg/100 mL culture medium). Our results were developed using RIA, ELISA, and Lowry methods. ANOVA was used for statistical analysis. *We found that* after *in vivo* treatment, each sweetener modulated the basal OT secretion of NH cultures in a downward direction, which was followed by a stronger decrease in OT secretion after *in vitro* treatments at the contact cell level. When these data are compared with the AVP release results, it can be seen that OT secretion is more sensitive to the applied sugar substitutes than AVP. The experiments seem to confirm an endocrine modulating effect, which justifies further studies (supported by EFOP-3.6.1-16-2016-00008, EFOP3.4.3-16-2016-00014; TAMOP-4.2.4.A/2-11/1-2012-0001).

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EP660

Systematic evidence mapping of thyroid hormone patterns after exposure to endocrine disrupting chemicals in adult rodents

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Certain endocrine disrupting chemicals (EDCs) are known to disrupt the thyroid hormone system. Thyroid hormone (TH) levels are physiologically regulated by the hypothalamic–pituitary–thyroid (HPT) axis, a tight feedback loop, whereby low levels of T4 stimulate an upregulation of TSH, and conversely if T4 levels are raised. Low levels of T4 (with chronic upregulation of TSH) can lead to thyroid hyperplasia – an outcome that is recognised by regulatory groups for substances of concern to human health. In pregnant women, even acute exposure resulting in low T4 can lead to cognitive deficits in the foetus. While most chemicals disrupt the TH system by lowering T4 levels, some chemicals lower T4 but without a concomitant increase in TSH or may lower TSH as well. We were interested to investigate the different TH patterns seen after exposure to various EDCs, towards an understanding of the different mechanisms of action (MoA), we therefore conducted an extensive systematic evidence mapping exercise. We used the PECO method and included published studies that measured T4/T3 and TSH in adult rodents aged ≧ 6 weeks at the life stage of dosing. All chemical classes were included, with their exposure by gavage. Results were collated for T4/T3 and TSH measurements. We found that chemicals were mainly able to decrease T4 together with the expected increase in TSH, suggesting that the feedback loop is unaffected; although chronically unregulated levels of thyroid hormones have adverse health effects. However, some chemicals are able to decrease T4, but also decrease TSH or cause no change in TSH, thereby disrupting the feedback loop and causing apparent central hypothyroidism. EDCs can act on different molecular targets within the TH system such as transporters, enzymes and receptors in different parts of the TH system, including acting on hepatic enzymes to expedite the excretion of THs via the liver. The mechanisms by which various chemicals disrupt the TH system have not yet been fully identified for different chemical classes. Current regulatory tests for market placement of chemicals require T4 measurement, with the assumption that TSH is raised. We find that this is not the case for many chemicals and therefore the complexity of EDC MoA needs to be considered in the testing strategy in order to identify chemicals that are potentially damaging to human health.

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EP661

Endocrine complications in patients of beta thalassemia major

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Introduction

Endocrine complications are common in beta thalassemia major (BTM) patients receiving blood transfusions. Chelation therapy has a role in preventing such complications. However, patients may have difficulties adhering to chelation therapy. We aimed in this study to determine the endocrine complications in BTM patients.

Methods

This was a descriptive study with cross-sectional data collection over a 6 month period from February 2022 to July 2022, including 43 patients with BTM follow up at Haematology department of Rabta Hospital. The patients underwent a clinical examination and a fasting blood sample was collected for biological measurements.

Results

The mean age was 27 ± 4.78 years. The median duration of erythrocyte transfusions was 25.9 ± 4.75 years. The patients were transfused at a rate of 2 transfusions per week in 65% of cases. Mean ferritin level was 1542.2 ± 594.7 μg/l. Ferritinemia greater than 1000 μg/l was observed in 32 patients (74%). One endocrine complication was found in 35 patients (81%), two endocrine complications was found in 13 patients (30%) and an association of three endocrine complications was found in 3 patients (7%). Fifteen patients developed hypothyroidism (35%). The mean age of patients with hypothyroidism was statistically higher than those with euthyroidism ($P = 0.023$). Diabetes mellitus was found in 14 patients (33%) and prediabetes in 8 patients (19%). BTM patients with prediabetes had statistically higher mean level of ferritinemia ($P < 0.01$). Two

patients developed hypoparathyroidism (5%) and nineteen developed hypogonadism (44%). Patients with hypogonadism had statistically higher mean level of ferritinemia ($P=0.049$). Finally, no cases of adrenal insufficiency were found.
Conclusion
The detection of endocrine and metabolic complications is essential during the follow-up of BTM patients. A monitoring of clinical and biological parameters makes it possible to detect early and sub-clinical abnormalities. Thus, patients will have an early and targeted management.

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EP662

Early Dinner instead of Late Night reduce the risk of endocrine as well as genetic disruption

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Background
Our bodies function optimally when we align our eating & sleeping patterns with our circadian rhythms, the innate 24-hour cycles that tell our bodies when to wake up, when to eat and when to fall asleep. Chronically disrupting this rhythm by eating late night meals & sleep could be a recipe for Hypertension, CVD, and metabolic trouble.
Aim and objective
The aim of this study is to investigate whether there was a relationship between morningness(MC) (110n) intermediate(IC) (100n) & eveningness chronotype(EC) (35n) in T2DM.
Methods
A total of 245 subjects' age 18 to 60 years were recruited in Clinical OPD of General Medicine, KGMU. We have tested FBG & PP level, lipid profile HbA1c, Insulin, Leptin and Cortisol level, 48 h ABPM.
Result
When we compared these 3 groups, Significant Different parameters found in FBG ($P=0.01$) Postprandial ($P=0.03$) HbA1c ($P=0.001$) TG ($P=0.0001$), Total Cholesterol ($P=0.01$) & VLDL ($P=0.005$). It also shows the complete inversion of the cortisol level (0.003). Insulin, IL-1 beta & IL-6 also show significant change in late night eating T2DM Patients. Systolic/Diastolic readings of ABPM shows significant change between MC and IC (0.005) but not b/w EC & IC (0.007). And for reliability of sleep by actigraphy shows MC (6:15 $\pm$ 1:35) & EC (8:18 $\pm$ 1:23) take complete sleep but IC total sleep hours (5:10 $\pm$ 1:05) are very less. Disruption of Rev Erb (0.003) & Ror α (0.001) gene expression is also a risk factor for Cardio metabolic Diseases in T2DM patients.
Conclusion
Intermediate & Eveningness type are more likely to have late night eaters & they are associated with greater risk of Metabolic Disorders like Dyslipidemia, T2DM & CVD as well as disruption in circadian expression.

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EP663

Eating as well as sleeping later or modification of lifestyle can promote a negative profile of endocrine hormones & inflammatory markers

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Background
Our bodies function optimally when we align our eating & sleeping patterns with our circadian rhythms, the innate 24-hour cycles that tell our bodies when to wake up, when to eat and when to fall asleep. Chronically disrupting this rhythm by eating late night meals & sleep could be a recipe for Diabetes, CVD, and metabolic trouble.
Aim and objective
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Conclusion
Intermediate & Eveningness type are more likely to have late night eaters & they are associated with greater risk of Endocrine & Metabolic Disorders like Dyslipidemia, T2DM & CVD.

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EP664

Relationship between perceived stress, hair cortisol and burnout components in health workers during the second year of Covid 19 pandemic

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In Wuhan China in December 2019, cases of severe atypical viral pneumonia emerged, and the World Health Organization declared COVID-19 a pandemic. In this critical context, health workers were on the front lines, directly participating in the evaluation, diagnosis, and treatment of patients with COVID-19. The objective of our work was to evaluate stress and burnout in health workers and to measure hair cortisol levels as a stress biomarker during the second wave.
Materials and methods
496 health workers were included from Cosme Argerich Hospital ($n=190$), "José de San Martín" Hospital de Clínicas ($n=156$) and Carlos G Durand Hospital ($n=150$). Sociodemographic data of the included individuals was gathered, completing the following psychometric tools: perceived stress, social support, burnout scale, anxiety scale. Hair samples were obtained from posterior vertex between July and October 2021. Hair cortisol was measured following the procedure developed in our laboratory with an automated chemiluminescent method (Immulite 2000).
Results
Table 1 shows the associations found in the studied population. 11% ($n=54$) presented Burnout (High Emotional Exhaustion, low Personal Achievement and high Depersonalization). It was observed that the two Acute Care Hospitals (Argerich and Durand) presented a similar Burnout percentage (13%, $n=25$; 12%, $n=18$, respectively), whereas it was lower in the University Hospital (7%, $n=11$). When we performed a binary logistic regression, we found that Perceived Stress, Anxiety and age were associated with Burnout ($P=0.024$, OR: 1.258 [IC1.030–1.536]; $P=0.025$ OR: 0.894 [IC0.810–0.986]; $P=0.001$ OR: 0.954 [IC0.926–0.981], respectively). Considering individuals with hair cortisol levels above median, a significant association was observed between hair cortisol and age, hours worked, Emotional Exhaustion and Depersonalization ($r=-0.236$, $P<0.0001$; $r=0.204$, $P=0.006$; $r=0.185$, $P=0.006$; $r=0.172$, $P=0.010$).
Conclusion: In this work conducted during the second wave of COVID-19 pandemic, it was observed that Burnout was associated with low social support, high personal exhaustion and younger age. Burnout percentage found during the second wave in Hospital de Clinicas was significantly lower than the one obtained in July 2020. Health workers are especially exposed to stress and burnout, being a

vulnerable population to psychological distress. Therefore, strategies should be implemented to assess this psychological emergency.

Table 1 Statistical Associations

Variable	Anxiety	Burnout		
		Emotional Exhaustion	Personal Achievement	Depersonalization
Hair Cortisol	NS	$r=0.129$, $P=0.005$	NS	NS
Perceived stress	$r=0.240$, $P<0.0001$	$r=0.269$, $P<0.0001$	NS	$r=0.102$, $P=0.026$
Workload	NS	$r=0.228$, $P<0.0001$	NS	NS
Anxiety	NS	$r=0.300$, $P<0.0001$	NS	NS
Social support	NS	NS	$r=0.183$, $P<0.0001$	NS

*NS= not significant

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EP665

Psychosocial profile of transgender population attended in a gender identity unit

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Introduction
Transgender people are a diverse population affected by a variety of negative health indicators. Studies report, among other conditions, a high prevalence of mental health problems and substance abuse. However, there are still health issues that have been poorly analyzed and long-term longitudinal follow-up studies are scarce.
Objective
The aim of this study is to deep into the demographic characteristics and the psychosocial profile of transgender people attended at the Gender Identity Unit of Hospital Puerta del Mar (Cadiz), as a provincial reference unit.
Materials and methods
This is a descriptive cross-sectional study with data collected during the first visit to the psychology consultation between January of 2019 and December of 2020. 21% of transgender people treated in our unit requested an assessment by a clinical psychologist. The endocrinologist is responsible for making the referral to the psychologist if necessary. Demographic variables and other parameters of the psychosocial sphere are analyzed.
Results
Of the 124 people included in this study, 53% were transwomen and 47% transmen. The mean age was 20.54 ± 6.85 years. Regarding the level of studies, 3.4% had primary studies, 45.7% secondary studies, 27.6% higher studies and 23.3% vocational training. Family support was recognized by 85.5% of the population and 37% had a partner. 46.2% declared bullying in the social field. Gender incongruence began in childhood in 59.1%. Gender affirming hormones have been started in the 31.2% of people analyzed. Reasons for consultation were: anxious-depressive symptoms in 22% of the cases, doubts about gender affirming hormones in 14.4%, family non-acceptance in 6.8%, psychological support in 33.3%, gender dysphoria in 5.3%, various requeriments 6.1% and others in 11.4%. The attitudes most frequently taken on the first visit were: psychoeducation in 31.8% of the cases, family therapy in 5.3% and support in 51.5%.
Conclusions
In our setting, transgender people who request a follow-up in a clinical psychology consultation are mainly young people, with a history of gender incongruence since childhood and a frequent history of bullying. The reasons for the assitance demand are mainly the accompaniment in the gender reassignment process and the management of anxious-depressive symptoms.

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EP666

Methods for assessment of the mitochondrial toxicity by toxicant with murine kidney stem cell

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Mitochondria play an important role in generating energy, and they are essential to cell survival. Mitochondria have varieties of functions, such as regulating intracellular calcium concentration and signal transduction, controlling hormone synthesis, inflammatory responses, and free radicals. In particular this research is interested in the mitochondria in kidney tubular cell. Since mitochondria in tubular cells play an important role in supplying energy, removal of waste and reabsorption of nutrients in the blood, control of blood pressure, and maintenance of homeostasis. Mitochondrial damage may occur by drugs or related chemicals for the treatment of various diseases. Therefore, it may be related to mitochondrial dysfunction. Following experiment was conducted to investigate the relation between kidney and mitochondrial dysfunction. First, five drugs known to be toxic chemicals to mitochondria were selected. After treatment with mouse kidney stem cells, the specific concentration of cell viability (IC50) was selected for each chemicals. The results of valproic acid, a representative mitochondria toxicant, treated on the cell, confirmed that the expression of SOD2 increased according to the increasing concentration of valproic acid. Result of performing an analysis using MitoSOX red staining to confirm the relationship between mitochondrial toxicity and mitochondrial reactive oxygen species (mtROS), it was found that the level of mtROS according to the concentration of a valproic acid was relatively increased.

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EP667

Syndromic disorders with short stature

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Keywords: short stature, Noonan syndrome, Prader-Willi syndrome, Silver-Russell syndrome, genetic syndromes
Introduction
Short stature is one of the major components of dysmorphic syndromes. Growth failure may be due to a wide variety of mechanisms, either related to the growth hormone (GH)/insulin-like growth factor axis or to underlying unknown pathologies. At present, GH therapy is used in most syndromic disorders, although long-term studies evaluating this treatment are insufficient and some controversies exist with regard to GH dose, optimal age to begin therapy and adverse effects.
Objective
To study etiological, genetic and diagnosis aspects of children with dysmorphic short stature.
Methods
Retrospective study including 60 children and adolescents with syndromic disorders with short stature admitted in the Department of Endocrinology diabetology and nutrition. The related anthropometrics and laboratory examinations were assessed in all participants.
Results and discussion
We report 60 children and adolescents with short stature aged 14 ± 3.3 years, including 34 boys and 26 girls, were analysed in this study. The mean weight standard deviation score (SDS) and height SDS were -2.67 ± 1.28 and -4.06 ± 1.51 respectively. The majority of the children (56.9%) were prepubescent. The mean difference in bone age from chronological age was 25 months ± 9. A propranolol–glucagon test was evaluated in 48.3% of patients. The causes of syndromic short stature in our study are represented mostly by: malformation of the pituitary gland in 26.7% and Turner syndrome in 11.7%, followed by MOC (8.3%), prader wili syndrome (6.7%), Noonan's syndrome in 3.3%, 3M syndrome in 8.3%, waardenburg syndrome in 3.3%, russell-silver syndrome in 3.4%, DMC in 3.3%., and lastly 3A syndrom in 1.7%, Meier-Gorlin syndrome in 1.7%, as well as Eliis van Creveld syndrome. The genetic evaluation is still ongoing in 19.9% of the cases.
Conclusions
Genetic disorders are among major causes of short stature in children. Genetic testing is mandatory, in dysmorphic short stature. Patients should be referred to tertiary care centers for an individualized management.

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EP668

A bibliometric and qualitative analysis of the top 2500 most cited PCOS articles: Analysing global disparities in PCOS research and collaborations

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Introduction
Polycystic ovary syndrome (PCOS) is a complex condition with multi-systemic implications that can greatly impact patients' lives. To understand and deliver the varied needs of people with PCOS, a substantial onus lies on PCOS researchers to objectively study patient data and formulate evidence-based recommendations. Equitable research is crucial to ensure fair representation of people of various ethnicities and stratify population-specific analysis to have generalisable findings in policy papers and scientific research globally. The aim of this study is to quantify and study the variation and collaboration across geography in top 2500 most-cited PCOS peer-reviewed articles.
Methods
We screened all publications for the search query "Polycystic Ovary Syndrome" in the title or abstract to extract the top 2500 publications with the highest number of total citations using the software Dimensions®. We identified the authors and organisation/ hospital of practice of authors through their listed affiliations. Countries of practice were further classified into high-income, lower-middle income, upper-middle income, or low-income countries(LIC) based on the 2022 World bank report. Vos Viewer® was used to analyse bibliometrics and analyse total link strength between various categories. Network visualisation was done to analyse co-authorship between researchers' countries of practice. Similarly, overlay visualisation was used to study collaborations over time. Mann Whitney U-test was done to study the total link strength in co-authorships in HICs and LMICs with $P < 0.05$ considered as statistically significant.
Results
The authors of the top 2500 of 28 901 most cited articles for PCOS with 396 040 citations(59.5% of the total citations) were from 62 countries(40 HICs, 15 UMICs, and 7 LMICs). The United States had the highest number of total publications(847) and citations(155 590) followed by UK(324 publications with 54 451) and Australia(186 publications with 37 042). Only 3/54 African countries and no low-income countries were identified as the researchers' country of practice. For PCOS research, HICs had higher link strength than LMICs($P = 0.007$). We found only 3 clusters with a total 448 links between countries in the network visualisation with a total link strength of 1310. In overlay visualisation, collaborations during the last decade were noticed between some HICs and MICs including Lebanon, Egypt, India, Sri Lanka, and China.
Conclusion
Our study shows the limited global representation of MICs and LICs in the most impactful PCOS research by total citations. This highlights the need for more extensive partnerships and networks, particularly with researchers from LMICs to increase the representation of PCOS research globally.

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Pituitary and Neuroendocrinology

EP669

Pituitary apoplexy triggered by COVID-19?

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Introduction
Pituitary apoplexy is a rare and potentially life-threatening disorder defined by hemorrhage or infarction of the pituitary gland. Occasionally, it may be the first manifestation of an underlying adenoma.
Case report
We present a case of a 70-year-old male, who was admitted in our clinic for an incidentally discovered pituitary macroadenoma accompanied by severe left hemicrania, otalgia and left eyelid ptosis.
Medical history
Two weeks ago, the patient was hospitalized for SARS-COV2 infection, with a moderate form of pneumonia and was administered anticoagulation and glucocorticoid therapy, antipyretics, rehydration fluids, no intubation needed.
During that stay, he suddenly developed a vertebrobasilar syndrome, which prompted an imagistic evaluation, revealing a pituitary macroadenoma with optochiasmatic and cavernous sinus compression, with no signs of acute bleeding or intracerebral lesions, thus excluding a stroke/brain hemorrhage.
Admission to endocrine clinic
Clinical examination showed pale skin, multiple post-anticoagulation hematomas, a remitting left eyelid ptosis, unstable gait, narrowed visual field, no polyuria or polydipsia.
Biological assessment identified microcytic hypochromic anemia, normal platelet count, inflammatory syndrome, elevated D-dimer level, low iron level.
Endocrine evaluation revealed pituitary insufficiency(adrenocorticotropic, tireotropic and gonadal) with a bilateral narrowing of the peripheral visual field.
The pituitary contrast MRI revealed a macroadenoma(21/17/20 mm)within a precocious subacute state hemorrhage with optochiasmatic and cavernous sinus compression. Since the patient was hemodynamically stable, conscious and further evaluations didn't show signs of worsening, we opted for conservative management and corticotherapy. Patient was discharged with improved evolution, and under hormonal therapy.
Second endocrine admission
After two weeks, he was readmitted urgently for severe headache and right eyelid ptosis. We initiated glucocorticoid therapy in anti-inflammatory doses, with remission of clinical symptoms. The second MRI showed a shrinking macroadenoma(18/17/17 mm) with no rebound hemorrhage. During this stay, patient accused mild discomfort in his left iliac region, rapidly progressing to severe pain, with abdominal muscle defense, inflammatory syndrome and increased markers of sepsis. He was sent for exploratory surgery and diagnosed with an abscessed hematoma of the left iliopsoas muscle compartment. The patient was released with a positive outcome and reevaluated regularly.
At 3 months, MRI showed a much smaller adenoma(18/7/15 mm), with withdrawn hemorrhage.
Conclusions
As awareness of COVID-19-associated coagulopathy increases, thrombotic manifestations are implicated in mortality. This case report unveils a rare and never cited before, association between two life-threatening pathologies, that could both be linked to anticoagulation therapy and/or prothrombotic status.

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EP670

Carney complex as a rare reason of acromegaly in adulthood

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Carney complex is a rare hereditary syndrome with an autosomal dominant inheritance pattern that manifests itself with a set of specific symptoms. Case presentation. 32-year-old woman was admitted to the endocrinological hospital with an active stage of acromegaly. From the anamnesis it is known that at the age of 11, the height was 172 cm. The diagnosis of acromegaly was established at the age of 28 years: IGF-1 673.8 ng/ml (78–311), pituitary gland with para(d)-sellar spread (11×13×9 mm). She did not receive prescribed somatostatin analogs. At the present examination at the age of 32 years: acromegalic clinical features, no skin leisures, weight 71.6 kg, height 173.5 cm, IGF-1 – 475.8 ng/ml, pituitary adenoma was the same size. The examination also revealed endogenous ACTH-independent hypercortisolism: an increase in salivary cortisol (evening) – 11.86 nmol/l (0.5–9.65) and free cortisol in daily urine – 1485.8 nmol/day (100–379), a decrease in ACTH – 1.2 pg/ml (7.2–63.3), according to MSCT – a picture of nodular hyperplasia of both adrenal glands. At the age of 25, she was observed for euthyroid multinodular goiter, at the onset, TAB – Bethesda II was performed, during the present examination, an increase in the node size the left lobe to 15× 16×33 mm was noted, with TAB Bethesda IV.
At the age of 27, resection of the left mammary gland was performed due to fibrocystic mastopathy and intraductal papilloma. At the age of 29 years, echocardiography showed a left atrial myxoma, which was surgically removed with histological confirmation of this type of tumor. Given the young age of the patient and the onset of the disease, the presence of multiple neoplasia, heart myxoma in anamnesis and in mother, a genetic study was carried out: in the *PRKAR1A* gene (NM_212472.2) in the 8th exon, a previously undescribed variant was found (HG38, chr17:68527885delAA, c.755_756del) in the heterozygous state, leading to a deletion of two nucleotides and a shift in the reading frame of p.K252Sfs*17 with a coverage depth of 210×. The variant does not appear in the gnomAD population frequency database. The variant most likely results in the loss of function of the corresponding copy of the gene.

The patient was successfully operated on pituitary adenoma. Of thyroid tumor and Cushing's syndrome, the patient refused. The study of the variability of the components of this syndrome should help various specialists diagnose a rare hereditary pathology.

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EP671

Medical complications of craniopharyngioma management in a uk tertiary pituitary centre

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Background
Craniopharyngioma (CP) is a rare sellar or suprasellar epithelial tumour with a prevalence of approximately 2 per million and it occurs either in childhood between the ages of 5 and 14 years or in adulthood between the ages of 50 and 74 years. Histologically, CPs are divided into adamantinomatous, more prevalent in children, and papillary, more prevalent in adults. They are usually benign, but rare cases of malignant CPs have been reported. Clinical presentation is usually with symptoms of hypothalamic involvement such as weight gain, disturbance of circadian rhythm, disorders of temperature or thirst regulation, deficiencies of pituitary hormones, visual disturbances, or hydrocephalus. Neurosurgical resection is the treatment of choice but may need to be followed by radiotherapy in case of incomplete resection or tumour recurrence.
Aims
To assess the prevalence of post-operative medical complications in patients with CP in our institution and compare the findings with similar published series of patients from other centres.
Methods
We reviewed the documentation, correspondence, and biochemical records of 82 patients with CP who operated on between 2002 and 2022 at the University Hospital Southampton NHS Foundation Trust, UK. The patients had undergone either open or endoscopic resection of their CPs. Evaluated post-surgical outcomes included growth hormone deficiency, secondary hypothyroidism, hypocortisolism, hypogonadism, arginine vasopressin (AVP) deficiency, hypopituitarism (> 1 hormonal deficiency were present), hypothalamic damage and cerebrospinal fluid (CSF) leak.
Results
In our cohort, 16% of patients (13/82) had a hormonal deficiency at presentation. 62% of patients (51/82) developed new-onset hypocortisolism post-surgery (the commonest hormonal deficiency observed), followed by secondary hypothyroidism in 48% of patients (39/82; one case of late-onset secondary hypothyroidism due to pituitary radiotherapy). AVP deficiency was noted in 39% of patients (32/82), secondary hypogonadism in 32% of patients (26/82) and growth hormone deficiency in 24% of patients (20/82). 59% (48/82) had more than one hormonal deficiency i.e., hypopituitarism and 15% (12/82) had hypothalamic dysfunction manifesting as obesity, sleep-wake disturbance or delayed puberty. 45% (37/82) required adjuvant radiotherapy and in 18% of patients (15/82) the tumour recurred. The commonest surgical complication was CSF leak in about 10% of patients (8/82).
Conclusion
Post-operative hormonal deficiencies are very common in patients undergoing neurosurgical intervention for CPs and it is often a direct unavoidable consequence of surgery in patients without endocrine anomalies at their initial presentation. The findings in our cohort of 82 patients are consistent with similar published series in the literature.

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EP672

Early Left Ventricular Diastolic Dysfunction in Females with Chronic Hyperprolactinemia: a Doppler Echocardiographic Study

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Despite the myocardial prolactin (PRL) binding activity and the known effect to enhance contractility in the isolated rat heart, little information is available concerning the cardiovascular consequences of hyperprolactinemia in humans. To elucidate the effects of chronic hyperprolactinemia on cardiac structure and function, twenty-four patients with isolated PRL-secreting adenoma and twenty-four controls underwent a complete mono- and two-dimensional Doppler echocardiography. Blood pressure and heart rate were similar in the two groups, and no significant differences were observed as to left ventricular (LV) geometry between patients and controls. Resting LV systolic function was normal in patients with hyperprolactinemia, as shown by similar values of fractional shortening and cardiac output. Conversely, hyperprolactinemic patients exhibited a slight impairment of LV diastolic filling, as demonstrated by the prolongation of the isovolumetric relaxation time and the increase of the atrial filling wave of mitral Doppler velocimetry (58 ± 13 vs 47 ± 8 cm s^{-1}, $P < 0.05$) with a subgroup of females (16%) having a clear diastolic dysfunction, and a worse exercise capacity (6 min walking test 452 ± 70 vs 524 ± 56; $P < 0.05$). In conclusion, hyperprolactinemia in humans may be associated with slight impairment of diastolic function, with an overt diastolic dysfunction in a subgroup of females which correlated with poorer exercise performance, in the absence of significant abnormalities of LV structure and systolic function.

Table 1 Echocardiographic parameters and physical performance in controls and hyperprolactinemic subjects.

	Hyperprolactinemia $n=24$	Control $n=24$
Aortic root (mm)	30 ± 3	28 ± 3
Left atrium volume index (ml/m^2)	27 ± 7*	22 ± 6
IS diastole (mm)	9 ± 2	9 ± 1
PW diastole (mm)	8 ± 7	8 ± 1
LV-EDD (mm)	48 ± 3	48 ± 3
LV-ESD (mm)	29 ± 3	29 ± 3
LV Mass (g)	163 ± 52	169 ± 40
Fractional shortening (%)	39 ± 5	39 ± 5
LV ejection fraction (%)	61 ± 3	60 ± 2
Cardiac output (l/min)	5.3 ± 1	5.5 ± 1
TAPSE (mm)	22 ± 4*	25 ± 3.6
Peak TR velocity (m/sec) IRT (ms)	2.5 ± 0.6* 93 ± 15	2.1 ± 0.4 75 ± 9
IRT (ms)	93 ± 15	75 ± 9
Mitral DT (ms)	147 ± 28	142 ± 27
Mitral E/A ratio	1.44 ± 0.46*	1.66 ± 0.25
Mitral E/E' ratio	7.8 ± 1.9*	6.4 ± 2.0
LV diastolic function:		
normal diastolic function (n, %)	14 (58.4)*	23 (95.8)
undetermined function (n, %)	7 (29.1)*	1 (4.2)
diastolic dysfunction (n, %)	3 (12.5)*	0 (0)
6 MWD (m)	515 ± 60*	610 ± 54

IS = interventricular septum; body surface area; PW = posterior wall; LV = left ventricular; EDD = end-diastolic dimension; ESD = end-systolic dimension; IRT = isovolumic relaxation time; DT = deceleration time; E = mitral early peak flow velocity; A = mitral late peak flow velocity; 6 MWD: 6 min walking distance; * = $P < .05$ vs controls.

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EP673

Hyponatraemia post endoscopic pituitary surgery: A tertiary centre experience of a large cohort

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Post-pituitary surgery hyponatraemia (HN, sodium < 135 mmol/l) is relatively common and may result in prolonged hospitalisation. Herein we report a retrospective analysis of our experience in a tertiary institute. We conducted a retrospective case note review of **318** patients (M 54%, F 46%, mean age 58 years) 65.7% non-functioning adenoma (NFA), 10% somatotropinoma, 5% prolactinoma, 11% corticotropinoma (half were clinically silent), 8% craniopharyngioma, and 0.3% FSHoma, who underwent endoscopic transphenoidal surgery between 2019 and 2022. Of those 28 patients (19F, 9M) developed post-surgery HN (9% of total), of whom 54% were above 70 years of age, 61% with NFA and 18% with corticotropinoma. Of those with

HN, 39% developed it within 1–3 days of surgery and 61% between 5 and 10 days. The majority had no evidence of prior hormone deficiency (61%), while 36% had pre-operative HN. The severity of HN as follows: mild (130–135 mmol/l) 7%, moderate (125–129 mmol/l) 61% and severe (<125 mmol/l)32%. The majority (68%) were on a pre-operative medication that can cause low sodium including: diuretics, ACE inhibitors, angiotensin receptor antagonists, proton pump inhibitors and antidepressants. Only 9 of 318 total patients undergoing pituitary surgery (2.9%) required readmission due to HN and that is 32% of hyponatraemia cases, most of whom had pre-operative HN or on medication that can caused it, with 54% having HN resolved within 3 days, and 32% within 5–7 days. The management of post-operative HN consisted of 43% fluid restriction (FR) alone, 32% FR and oral sodium tablets, 18% FR and medication review, 15% 1.8% sodium infusion and remaining had a combination of interventions. Our HN incidence is lower than some of the published large cohorts, mostly mild-moderate and not requiring hospital readmission. We have identified several predictive risk factors for development of post-surgery HN: pre-operative sodium, medications, advanced age and female gender, and thus proactive risk mitigation may reduce its occurrence and readmission rate.

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EP674

Tolvaptan in the management of severe hyponatremia associated with acute intermittent porphyria

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Background
Acute intermittent porphyria (AIP) is an inherited autosomal dominant disorder characterized by hepatic deficiency of hydroxymethylbilane synthase (HMBS) /porphobilinogen deaminase (PBGD), the third enzyme of the heme synthesis pathway. Hyponatremia is one of the main presenting symptoms and it is thought to be related to an inadequate secretion of ADH (SIADH). Since AIP is an uncommon disease, there is little information about how AIP related hyponatremia responds to standard treatment.
Case presentation
We report the case of a 51−year−old woman who got admitted to the emergency room for acute abdominal pain and dizziness. Physical examination and laboratory tests showed a severe euvolemic hyponatremia with serum sodium (SNa) 119 mEq/l, urine osmolarity 933 mOsm/l and urine Na 149 mEq/l, all of them compatible with SIADH. A sodium chloride 3% infusion at 0.5 ml/kg/h was started. SNa rose to 121 mEq/l after 24 h. In the following days SNa stabilized at 121–122 mEq/l despite water intake restriction, and tolvaptan was started. Following our standard treatment protocol for SIADH related hiponatremia, we started with a tolvaptan dose of 7.5 mg. SNa increased to 122 mEq/l at 24 h and tolvaptan was increased to 15 mg/day on the second day. Without further dose increment, SNa progressively reached normal values within five days. As the patient complained of abdominal pain, AIP was suspected and a Hoesch test confirmed the diagnosis. Treatment with hemin was started, which improved the patient 's clinical signs and normalized the δ-aminolaevulinic acid (ALA) and porphobilinogen (PBG). SNa further increased to 142 mEq/l and tolvaptan was progressively decreased and finally discontinued, with SNa manteined in normal range thereafter.
Discussion and conclusion
As treatment of acute porphyria attacks is mainly based on intravenous administration of glucose 10% and/or human hemin, previous correction of hyponatremia is of paramount importance to avoid further decrease of SNa caused by large amounts of glucose solutions. In our case, the time frame for response to tolvaptan and the dose needed to achieve eunatremia were similar to those for SIADH-associated hyponatremia from a different origin. Thus, tolvaptan is an effective option to guarantee a desired serum sodium increase during acute porphyria attack to safely permit handling high volumes of glucose solutions. Standard protocols for treatment of SIADH related hyponatremia with tolvaptan can be applied to AIP; however, the treatment will only be maintained for the duration of the acute condition.

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EP675

Metabolic and surgical outcomes of adult patients with craniopharyngiomapatients undergoing extended transsphenoidal surgery (ETS) at a referral center

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Objectives
To describe the metabolic and surgical outcomes of adult patients with craniopharyngioma undergoing extended transsphenoidal surgery (ETS). Secondary: to compare surgical outcomes with patients undergoing conventional transcranial surgery (CTS).
Methods
Retrospective observational study. Adult patients with craniopharyngiomas undergoing ETS between 2015 and 2020 were included. Descriptive analysis was performed by obtaining median and quartiles for quantitative variables and frequency for qualitative variables. For the comparison between groups, a matched cohort of patients with craniopharyngioma who underwent CTS was used and a Fisher test was performed for qualitative variables.
Results
$n=16$. Male = 7(43.8%); age = 52.5(37.7–66) years. Follow-up time = 44.5(30–63) months. BMI pre-surgery = 26.01(22.72–28.51)kg/m2. The BMI increase at first year after surgery was 18.14%(7.2–24.26%). Obesity was present in 56.5% at first year post-surgery, although 77.7% were grade I (WHO classification). During follow-up, 25% developed type 2 diabetes and dyslipidaemia.
Conclusions
The most frequent metabolic complication after ETS in patients presenting with craniopharyngioma was obesity, present in 56% of patients in our study. Surgical complications were very frequent (93.8% and 92.8% one month and one year after surgery) due to the high rate of diabetes insipidus (98.8% and 85.7%) and hypopituitarism (87.5% and 78.5%). These data are consistent with the scientific literature and lower than with CTS. ETS compared to CTS reduces adipsia, seizures and psychiatric and surgical complications at first month and hydrocephalus, need for antiepileptic treatment and psychiatric complications at first year after surgery.

Table 1 Post-surgical complications at one month and one year post-ETS.

	First month post-ETS ($n=16$)	First year post-ETS ($n=14$)
Complications after surgery	15(93.8%)	13(92.8%)
Diabetes insipidus	15(93.8%)	12(85.7%)
Adipsia	0(0%)	1(7.1%)
Panhypopituitarism	14(87.5%)	11(78.5%)
Hypothyroidism	15(93.8%)	13(92.8%)
Adrenal insufficiency	17(87.5%)	12(85.7%)
Hydrocephalus	11(32.4%)	1(7.1%)
Seizures/anti-epileptic treatment	1(6.3%)	1(7.1%)
Cerebrospinal fluid fistula	1(6.3%)	0(0%)
Central nervous system infection	3(18.8%)	0(0%)
Visual disturbances	9(56.3%)	7(50%)
Psychiatric disorders	1(6.3%)	1(7.1%)
Neurological disorders	3(18.8%)	4(28.5%)

Table 2 Surgical complications in which significant or near-significant differences were obtained between patients undergoing ETS vs CTS.

		ETS	CTS	*P*
At first month	Adipsia	0(0%)	7(20.6%)	0.05
	Seizures	1(6.3%)	11(32.4%)	0.03
	Psychiatric disorders	1(6.3%)	12(35.3%)	0.021
	Neurological disorders	3(18.8%)	7(50%)	0.023
At first year	Anti-epileptic treatment	1(7.1%)	11(39.2%)	0.03
	Psychiatric disorders	1(7.1%)	12(42.8%)	0.018
	Hydrocephalus	1(7.1%)	9(32.1%)	0.075

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EP676

Early postoperative growth hormone measurement as a predictor of surgical remission of acromegaly

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Purpose
To evaluate the value of early postoperative growth hormone (GH) as a predictor of surgical remission of acromegaly.

Methods
We conducted a retrospective search through our database of patients who underwent transsphenoidal surgery for GH-secreting pituitary adenoma from 2011 to June 2022. Only patients who underwent the first pituitary surgery and had GH measurements on the fifth postoperative day were included. The surgical remission was defined as GH nadir <0.4 μg/l during an oral glucose tolerance test (OGTT) and normal insulin growth factor-1 (IGF-1) on the first follow-up three months after the surgery.
Results
We included 65 patients in the analysis with median FU of 31.5(3–155) months. Surgical remission was achieved in 44 patients (67.7%). Patients who achieved remission had significantly lower early postoperative GH levels (0.65 (0.06–8.92) vs. 3.61 (0.25–24.64), $P<0.001$). ROC analysis revealed a significant value of early postoperative GH on the prediction of surgical remission (AUC 0.832, $P<0.0001$), and the cut of GH ≤ 1.57 μg/l had a sensitivity of 90.9% and a specificity of 71.4%, respectively. No patients with an early postoperative GH ≤ 0.23 μg/l developed a relapse of acromegaly during the FU.
Conclusion
The early postoperative growth hormone measurement could be a reliable predictor of surgical and long-term remission of acromegaly.

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EP677

Prevalence and clinical characteristics of hyponatremia following pituitary surgery

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Introduction
Hyponatremia is one of the possible complications of pituitary surgery. Mild, asymptomatic hyponatremia can be managed with fluid restriction and oral supplementation, however more profound hyponatremia, especially when symptomatic, can be a reason for hospital readmission and often needs to be treated with saline infusion in ICU.
Aims
To estimate prevalence of hyponatremia and provide clinical characteristics in the cohort of patients who underwent surgery for tumour in sellar region at our centre.
Method
Single centre retrospective analysis of cohort of patients undergoing pituitary surgery in the past 30 months. Data of patients who had surgery for pituitary adenoma or other sellar tumor were analysed retrospectively. Those who developed hyponatremia in the period of 30 days following surgery were selected for further analysis. Preoperative radiologic features, patterns of sodium level changes, and endocrinological characteristics were noted.
Results
In the selected period, 313 pituitary surgeries have been performed at our centre. 23 cases of hyponatremia were identified of which 16 were women. Average age was 49 years (27–75 y). Pituitary adenoma was histologically confirmed in 15 cases of which 13 were macroadenoma. Four were hormonally active (one prolactinoma and three GH secreting adenoma). Other types of tumours involved 4 cystic lesions a 3 meningiomas. Suprasellar extension was present in 14 cases and parasellar extension in 12 cases. Six patients had early postoperative complication (four cases of CSF leakage and two haemorrhagic complications). Four patients developed early postoperative polyuria but in only one case diabetes insipidus reappeared after recovery from hyponatremia however it lasted only temporarily and the treatment with desmopressin was withdrawn subsequently.
In most of the cases hyponatremia was diagnosed on day 7 (39%, 9 cases, range 3–10 day). The lowest sodium on presentation was 118.9 mmol/l and during the treatment period the sodium nadir level observed was 113 mmol/l. Hyponatremia was symptomatic in 10 patients. Seven patients presented with neurological symptoms (seizures, vertigo, headache or confusion), three patients had gastrointestinal symptoms (nausea, vomiting). Thirteen patients were treated with 3% saline infusion while in the remaining cases treatment with oral salt tablets and fluid restriction was sufficient. Only two patients were treated as outpatient while the rest were readmitted and 9 of them were treated in the ICU. Only two patient developed diabetes insipidus after recovery from hyponatremia.
Conclusion
Hyponatremia was present in 7.3% cases while in only 2.8% hyponatremia was clinically and biochemically severe requiring admission to ICU.

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EP678

Endocrine side effects of immune-checkpoint inhibitors in patients with malignant melanoma

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Immune-checkpoint inhibitors have become important elements of oncology therapy in recent years. These monoclonal antibodies block immune-checkpoints, unleashing T cells to fight cancer. However, immune-checkpoints also play an important role in the prevention of autoimmune processes and immune-checkpoint inhibitor therapy can also trigger autoimmune adverse effects, termed immune-related adverse events. Endocrinopathies are among the most common immune-related side effects.
Objectives and methods:
We analysed data of 221 patients (131 males, 90 females, age 61.4 ± 13.3 years) retrospectively, who received immune-checkpoint inhibitor therapy for malignant melanoma at the Department of Dermatology since 2015 and we investigated endocrine side effects in these patients. Based on the obtained data, our aim was to develop a diagnostic guideline that can help to recognize endocrine side effects that develop during immune-checkpoint inhibitor therapy as soon as possible and to treat them appropriately.
Results:
Endocrine side effects occurred in 69 cases (31.2% of the patients). 58% of these patients were men, 42% were women and the average age was 61.4 ± 12.8 years. In 25% of the patients, the side effect appeared within one month after starting treatment, and in 89.1% within one year. 83.8% of endocrine side effects affected the thyroid gland, 16.2% isolated the pituitary gland, and 7.4% had side effects in both the thyroid and pituitary gland. We detected central hypadrenia in all patients diagnosed with hypophysitis. 36.2% of patients needed treatment due to endocrinopathy; discontinuation of immune-checkpoint inhibitor therapy due to an endocrine side effect was not necessary in any case.
Conclusions:
Endocrine side effects occurred in almost 1/3 of the patients receiving immune checkpoint inhibitor therapy. Based on the results of our study, endocrinopathies occur in a similar proportion in men and women, which means a difference compared to the female dominance observed typically in autoimmune thyroid diseases and autoimmune hypophysitis. Endocrine side effects occurred in 25% of cases after one month of immune-checkpoint therapy, this result highlight the need for screening in time in order to achieve timely diagnosis and administer appropriate treatment. It is particularly important to recognize hypophysitis, which can cause a life-threatening crisis in the case of untreated central hypadrenia.

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EP679

Epidemiologic and clinical characteristics of acromegaly in Russian hypothalamic and pituitary tumor registry (OGGO)

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Background
Pituitary disease registries are major instruments of epidemiological and clinical data collection used worldwide.
Objective
To assess the epidemiological and clinical characteristics of acromegaly in Russia according to Russian hypothalamic and pituitary tumor registry
Material and methods
Database of the Russian hypothalamic and pituitary tumor registry, which includes data from 84 regions of the country, was used for the study. Date of analysis – 01-Sep-2022.
Results
Currently there are 5054 patients with acromegaly in the registry. Prevalence per 100 000 inhabitants is highest in Kirov region (9.82), Karelia republic (9.48) and Vladimirskaya region (7.11). Annual incidence per 1 mil was 0.6 cases in 2021. Male to female ratio 1425(28.2%):3629(71.8%), median age 46.2 years [33.1;52.7], age at

diagnosis 46.2 years [33.1;52.7]. During the last visit, remission was recorded in 1671 patients (42.7%). Pituitary tumor size was available in 2131 patients: macroadenomas in majority of cases (1562 patients, 73.3%). Median IGF1 levels in patients with active disease was 378.0 ng/ml [245.9;620.0], basal GH 4.0 ng/ml [1.6;12.0]. Most prevalent complications were hypertension (47.8%), nodular goiter (31.6%), carbohydrate metabolism disorders (26.5%), obstructive sleep apnea (14.4%) and menstrual irregularity (12.1%). Interestingly, prevalence of joint diseases and colon polyps was quite low – 6.3% and 0.24%, respectively. Among all treated patients, 42.5% underwent neurosurgery, 13.9% – pituitary radiotherapy. Medical therapy, either monotherapy and combination, is registered in 42.3% of patients ($n=2140$): octreotide (75.3%), lanreotide (18.6%), pegvisomant (2.6%), cabergoline (18.7%) and bromocriptine (3.9%).Overall number of registered deaths in patients with acromegaly was 370 cases: 20 due to pituitary adenoma, 73 cardiovascular causes, 36 malignancies, 64 other causes and in 137 the cause was not specified.
Conclusions
Russian Hypothalamic and Pituitary Tumor Registry is a viable instrument for the assessment of epidemiological and clinical data, reflecting the implications of treatment strategies in real life practice. Median age of diagnosis in our study is similar to the literature data, however, other studies do not report female predominance, as seen in our cohort. Complication rates are mostly similar, however, extremely low prevalence of colon neoplasms and joint diseases shows that more effort should be put in the screening of these comorbidities. Remission rates and availability of neurosurgery are also lower than overall literature data, which shows the need for optimization in treatment strategies, as well as increase in data quality and registration.

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EP680

Clinical features and long-term follow-up of patients with Nelson syndrome: a case series presentation

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Background
Nelson syndrome is a rare complication of Cushing disease (CD), which occurs either in patients with very aggressive CD or as a result of misdiagnosis. Clinical characterization of patients with Nelson syndrome could provide important insights in management of the disorder.
Methods
We analyzed medical records of patients with CD between 2015 and 2021 to identify those who developed Nelson syndrome.
Results
Nine patients developed Nelson syndrome: 2 males and 7 females. Median age of CD onset 27.0 years [20.8;29;8]. Prior to adrenalectomy, 3 patients presented with macroadenomas, 5 – microadenomas, in 1 patient adenoma was not visualized. Seven patients received CD treatment before adrenalectomy: 5 patients underwent multiple transsphenoid neurosurgeries and radiation therapy, 2 were treated only surgically. Mean duration of CS before adrenalectomy was 62 months [48;89]. Mean duration between adrenalectomy and confirmation of Nelson syndrome was 25.5 months [18.5;36.3]. All nine patients developed Nelson syndrome: all had elevated morning ACTH levels – 1176 pg/ml [434;1713], pituitary tumor regrowth or visualization was seen in 6 patients, 4 patients presented with darkened skin tone, 3 – with severe headaches. Median follow-up duration after Nelson diagnosis was 28 months [17;75]. All patients received glucocorticoid replacement therapy – median dose 35 mg/day [25;35]. Three patients received medical therapy, either with cabergoline, long-acting octreotide or lanreotide. Combination of neurosurgery an pituitary radiation was used to treat 3 patients, 2 patients underwent only surgery and 2 received only radiation therapy. At last follow-up visit, 7 patients had pituitary adenoma remnant (5 macro-, 2 microadenoma): without further progression in 6 cases, 1 patient with tumor progression was referred for pituitary irradiation. In 2 patients no signs of regrowth was found on pituitary MRI. Median ACTH during last follow-up was 715.5 pg/ml [453.4;1173].
Conclusion
Nelson syndrome is a severe complication of CD which requires a strict long-term follow-up and all the treatment options to increase the chances of stabilization. In our cohort, combination of treatment modalities led to stabilization of tumor growth in 8 cases, however, ACT remained elevated in all patients. Further reports on this complication could help to identify optimal management strategies and improve the outcomes for Nelson syndrome.

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EP681

Prediction of the receptor phenotype of somatotrophic tumors and the effectiveness of the use of the first-generation somatostatin receptor ligands (fg-SRLs) in the long-term treatment of acromegaly

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The control of acromegaly with drug therapy (DT) by fg-SRLs is achieved only in 40–50% of cases, due to the heterogeneous composition of somatotrophic tumors. In order to optimize DT stratification of clinical and immunophenotypic biomarkers which make it possible to predict the long-term effectiveness of fg-SRLs at early stages is required.
The aim of the work was to assess the informativeness of pharmacotherapeutic testing (% of decrease of IGF-1 level after 3 and 6 months of treatment) for the prognosis of the receptor phenotype of a somatotrophic tumor and the rationality of DT by fg-SRLs.
Materials and methods
The comparative study included 33 and 47 patients with densely and sparsely granulated somatotroph tumors (DGST&SGST) who received postsurgical DT by fg-SRLs. Prolonged forms of lanreotide and octreotide were used. The duration of DT was 21.5 ± 21.8 months. The adequacy of DT was assessed by the level of IGF-1 index (IGF-1/ULN) ≤ 1. The control points were the indicators of IGF-1 before DT, after 3,6,12 months of treatment and at the last visit.
Results
The percentage of decrease of IGF-1 level after 3&6 months of fg-SRLs treatment was correlated with the expression of the SSTR2 ($r=0.44$; $r=0.36$), as well as the difference and the ratio between the SSTR2&SSTR5 [$r=0.46$; $r=0.46$&$r=0.41$; $r=0.43$;($P<0.05$)]. The final value of IGF-1 index in patients with DGST&SGST was 0.95 ± 0.27 vs. 1.4 ± 0.64, ($P=0.0002$). The magnitude of the decrease of IGF-1 level in the groups of patients with DGST and SGST after 3&6 months was 54.8 ± 19.6 vs. 28.4 ± 23.7% and 58.4 ± 18.0 vs. 31.6 ± 24.5%, respectively ($P=0.0002$). The presence of an inverse correlation between the percentage of decrease of IGF-1 level after 3&6 months of fg-SRLs treatment and the final value of IGF-1 index was revealed [$r=-0.59$; $r=-0.72$;($P<0.001$)]. In the ROC analysis, the AUC was 0.841&0.853. The decrease of IGF-1 level after 3&6 months by 46 and 49% of the baseline level was the cut-off point of effective DT. The sensitivity of these markers was 63&75%, the specificity was 79&80%, respectively. With a decrease of IGF-1 level after 3&6 months, over or under 50%, the final IGF-1 index was 0.9 ± 0.2 vs. 1.49 ± 0.62($P=0.000$).
Conclusions
1.The magnitude of the decrease of IGF-1 level after 3&6 months of fg-SRLs treatment reflects the severity of the expression of the SSTR2,as well as the intact postreceptor mechanisms in tumor cells.
2.The results of pharmacotherapeutic testing can be used as an additional predictor of the effectiveness of fg-SRLs long-term treatment.

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Abstract withdrawn

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EP683

Evaluation of the ACTH-CLU index for the differential diagnosis of ACTH-dependent Cushing's syndrome

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Introduction
Differentiation between Cushing's disease (CD) and ectopic Cushing's syndrome (ECS) remains a diagnostic challenge. Currently available tests lack sufficient sensitivity and specificity or are invasive and technically difficult. Recently, an ACTH-UFC index has been proposed to differentiate the two forms of ACTH dependent Cushing's syndrome (CS) (Ding, 2021). This work aimed to confirm the diagnostic utility of the ACTH-UFC index to differentiate CD from ECS.
Methods
Retrospective analysis of patients with ACTH-dependent CS seen at the Endocrinology Departments of Puerta de Hierro and Ramón y Cajal Hospitals between 1983 and 2021. The tests' diagnostic performance was evaluated by ROC curves. Gold standard for CD or ECS diagnosis was based on positive staining for ACTH in a tumor sample, remission of CS after tumor excision or inferior petrosal sinus sampling.
Results
80 patients were included (56 female, median age 43 years). 66 were diagnosed with CD (82.5%) and 14 with ECS (17.5%). Median plasma cortisol was 24 μg/dl at 0800 h, 21 μg/dl at 23 h, and 16 μg/dl after suppression with 1 mg dexamethasone, with no significant difference between both groups. Median UFC was 250 μg/day (887 μg/day in the ECS group Vs 221 μg/day in the CD group; $P<0.001$) and median plasma ACTH was 50 pg/ml (88 pg/ml Vs 48 pg/ml; $P=0.014$). The area under the ROC curve (AUC) for the ACTH-UFC index in predicting CD among ACTH-dependent CS was 0.852, lower than the 0.977 in the original study. The optimal cut-off value for the ACTH-UFC index was 1.0 (sensitivity of 68% and specificity of 93% to identify CD). In multivariate analysis, UFC showed an independent association with the diagnosis, with values >250 μg/day increasing the probability of ECS by 16.2 times ($P=0.01$). ACTH levels did not show this association. Accordingly AUC from isolated UFC was similar to that of the ACTH-UFC index (0.828). The exclusion from the analysis of cases with clinical evidence of ECS nullified the diagnostic utility of the ACTH-UFC index (AUC=0.652) and the isolated UFC (AUC=0.567). Nevertheless, diagnosing CD with an ACTH-UFC index ≤ 1 and ECS with an index $\geqq 28$, could save 63% of cases from additional testing, with a 98% certainty of correctly diagnosis.
Conclusions
ACTH-UFC index showed a worse diagnostic performance than referred and not superior to isolated UFC. In cases with greater diagnostic difficulty, neither of these tests were useful. However ACTH-UFC index could save more than 60% of cases from additional testing.

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EP684

Neuroendocrine regulation of fluid and electrolyte metabolism in patients after transnasal adenomectomy: can oxytocin be a potential hormonal prognostic marker of hyponatremia?

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Introduction
According to recent studies, fluid and electrolyte disturbances complicate the course of transnasal adenomectomy for pituitary adenomas in 13–30% of cases and are associated with a high risk of neurological complications and increased mortality. Neuropeptides discovered in recent decades (apelin, copeptin, oxytocin, brain natriuretic peptide) in many studies demonstrate their significant effect on the regulation of water-electrolyte metabolism, which makes them potentially important hormonal markers of its complications.
Aim
To study a neuroendocrine regulation of water and electrolyte metabolism in patients after transnasal adenomectomy and in cases of the development of hyponatremia.
Materials and methods
The study included the results of dynamic control of sodium and neuropeptides in 22 patients who underwent pituitary adenoma removal (inactive pituitary adenoma – 8 patients, acromegaly – 8 patients, Cushing's disease – 6 patients, 6 men and 16 women, median age 52 years [Q25 39; Q75 62]), 10 of whom developed hyponatremia (group 1) with a median serum sodium of 125 mmol/l, and 12 had no water–electrolyte disorders (group 2). In all patients, Na was determined in blood serum, as well as by ELISA apelin 12, copeptin, oxytocin and proBNP in plasma 24 h before surgery, 12–24 h, 3, 5 and 7–8 days after surgery.
Results
The analysis showed significant changes in oxytocin levels without significant changes in concentrations of other neuropeptides in hyponatremia. Spearman correlation analysis of simultaneous concentrations of oxytocin and sodium in the blood showed the presence of an association between the parameters in the postoperative period, which were manifested by the appearance of a positive correlation on day 3, and a negative correlation on days 5 and 7–8. When comparing oxytocin levels in the groups of hyponatremia and the absence of water–electrolyte disorders, statistically significant differences were revealed. The median concentration of this hormone in the hyponatremia group on day 7–8 was 2.1 times higher with hyponatremia – 6781 vs 3.199 ng/ml for the hyponatremia group and control, respectively ($P=0.002$ for the Mann–Whitney U-test)
Conclusions
Transnasal adenomectomy is the cause of severe hyponatremia in 7–18% of cases, in the pathogenesis of which, apparently, copeptin and oxytocin play a leading role, and the secretion of which has the character of inadequately elevated levels with the loss of a negative feedback with the concentration of sodium in the blood. At the same time, oxytocin has the potential to be a hormonal marker of this life-threatening complication.

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EP685

Weight gain in adult patients with suprasellar craniopharyngioma with varying degrees of hypothalamic involvement before and after the surgery

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Suprasellar craniopharyngiomas (CF) are characterised by a high incidence of involvement of the third ventricle, which determines the risk of hypothalamic obesity (HO). There are no unified diagnostic criteria for HO and its effective treatment. The assessment of pre- and postoperative hypothalamic damage is necessary for the choice of surgical strategy and early therapeutic intervention.
Objective
To estimate the incidence and extent of weight gain in adult patients with CF depending on the degree of hypothalamic involvement.
Methods
58 patients older than 18 years (30 women, 28 men), the median age 42 (range 29–54). All patients were operated, the degree of hypothalamic involvement was assessed on the basis of preoperative MRI and intraoperative data. The criterion for HO was a weight gain of 10 kg or more over a period of 6 months. Body weight was assessed before and after 3,6,12 months after surgery. Body mass index >25.0 for overweight (OW) and >30.0 for obesity (OB). By localizing tumor patients were divided into 2 groups: 1 – at "pituitary stalk" without penetration into the third ventricular cavity (24), 2 – combined "the pituitary stalk" and ventricular (34).
Results
In group 1: before the surgery OW in 25% cases (6), OB in 25% (6), weight gain was observed in 12% cases (3), the m?dian 5 kg (4–5). Total removal in 79% cases (19), of which in 12 patient the tumor was adhering to the third ventricle floor. After the surgery: OW in 25% cases (6), OB in 45%(11), HO developed in 30%(7), weight gain the m?dian 22 kg (15–27). In group 2: before the surgery OW in 32% cases (11), OB in 41%(14), HO in 29%(7), weight gain the m?dian 16 kg (14–18). Total removal in 61% cases (21). After the surgery: OW in 26% cases (9), OB in 64% (22), HO in 38%(13), weight gain m?dian 15 kg (12–25), of which only 2 had preoperative weight gain >10 kg. In both groups weight gain after surgery was observed within the first 6 months.
Conclusion
Preoperative HO was observed only among patients in 2 group, which in combination with MRI data can be regarded as an indication of hypothalamic involvement. Damage to the hypothalamus, due to tumor invasion or surgical treatment, causes weight gain of the same degree. After surgery, patients with a tumor with hypothalamic involvement but without pre-operative weight gain are at risk for HO.

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EP686

Inferior petrosal sinus sampling and stimulation with CRH: 18 years of experience in a tertiary hospital

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Background
Inferior petrosal sinus sampling (IPSS) is indicated in the diagnosis of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome (CS), especially when the results of the initial diagnostic tests are discordant.
Objective
To describe the patients who underwent this invasive functional test in a tertiary hospital.
Methods
This was an observational study of a retrospective cohort of patients with ACTH-dependent CS and IPSS between 2004 and 2022. We determined their epidemiological, hormonal, radiological and functional characteristics, and evaluated their diagnostic capacity and optimal cut-off points to differentiate between Cushing's disease (CD) and ectopic Cushing's syndrome (ECS).
Results
31 patients were evaluated. It was observed an ACTH secretion of a pituitary origin in 80% of cases and an ectopic origin in 20%. Patients with CD were more frequent female (64%) and those with ECS were mostly male (83.3%). There were no differences between age of diagnosis. Plasma cortisol, urinary free cortisol, and ACTH levels were higher in patients with ECS. Most IPSS were done before going to a definitive surgical treatment, so only 12.9% IPSS were done after surgery, meaning that persistence or recurrence of hypercortisolism was detected during follow-up. Regarding radiological findings, patients with IPSS gradient ACTH C/P compatible with CD (>2 basal or >3 after CRH stimulation) had a visible adenoma in 40% of cases, with a median size of 4 (2.5–5.0) mm. On the other hand, patients with a IPSS gradient of ECS had 33% cases of MRI positive, with a median adenoma size of 7 (7.0–7.0) mm.
Conclusion
ACTH-dependent CS can be a difficult entity to diagnose for clinicians. Clinical, biochemical and radiological characteristics of patients provide an approach to etiologic diagnosis but not in all cases. IPSS with CRH stimulation is a test with a high diagnostic accuracy and it is particularly recommended in patients with negative MRI or with adenoma smaller than 6–10 mm.

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EP687

ADH-deficiency (central diabetes insipidus) registry in Russia: current results

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Introduction
ADH-deficiency (central diabetes insipidus, ADH-D) is a rare disease, and data on worldwide and country-specific prevalence rates are scarce. ADH-D registries could provide valuable information on epidemiology, etiological distribution, treatment requirements and potentially serve as a guide for management decisions in clinical practice.
Objectives
To assess the epidemiological data on ADH-D in Russian Registry for Central Diabetes Insipidus (RCDI)
Materials and methods
Database of the Russian Registry for Central Diabetes Insipidus, which includes data from 42 regions. Date of analysis – 10-Sep-2022.
Results
Since previously reported data in 2018, the number of patients has increased from 2004 to 2971 patients with different etiologies of ADH-D. Highest prevalence is seen in Moscow region – 5.4 cases per 100 000 population. Male to female ratio: 1253(42.2%): 1718(57.8%), mean age at diagnosis 32.6 years. Among the identified etiologies the most common were postoperative (16%), pathology of development of hypothalamic–pituitary region (9.3%), head trauma (6.6%), tumors (5.4%) and hereditary forms of ADH-D (4.3%). Rare forms of ADH-D with less than 4% overall were neuroinfection, Langergans cell hystiocytosis, sarcoidosis, Sheehan syndrome, DIDMOAD syndrome and hypophysitis. Idiopathic ADH-D was registered in 42% of patients. Data on current therapy was available in 2657 patients. Most of the patients receive oral desmopressin ($n=1470$, 55.3%), followed by sublingual ($n=911$, 34.3%) and intranasal ($n=276$, 10.4%) forms.
Conclusions
Russian Registry for Central Diabetes Insipidus is a promising instrument for the assessment of epidemiology and treatment modalities in a rare endocrine disorder. Further efforts are made to include all the regions of the country and improve the data quality.

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EP688

The predictive value of IGF-1 in a cohort of children with growth hormone deficient and sufficient short stature

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Introduction
Insulin-like growth factor 1 (IGF-1) is an established serum marker for both diagnosis of growth hormone (GH) deficiency and for monitoring treatment with Somatropin, whether it is recommended for the classic GH-insufficient short stature cases or for other GH-sufficient disorders.
Aim
To evaluate whether serum level of IGF-1 at diagnosis has a predictive value for the response to somatropin treatment during the 2 years of treatment in children with both GH-deficient and GH-sufficient short stature.
Materials and methods
We performed a retrospective study which included 192 children treated with somatropin for at least 2 years with variate causes of short stature (mean age 8.02 ± 3.63, 71 boys, 121 girls). Patients were divided in GH-deficient and GH-sufficient based on peak GH value during stimulation tests with a cut off value of 7 ng/ml. Standard deviation score (SDS) was calculated for height and IGF-1 at diagnosis.
Results
SDS height gain at 2 years of treatment was positively correlated with SDS height gain at 6 months (r 0.549, $P<0.0001$) and 1 year (r 0.719, $P<0.0001$). SDS height gain at 2 years was negatively associated with male gender (beta -0.273, P 0.029) and baseline IGF-1 SDS (beta -0.249, P 0.001), after adjustment for age and diagnosis. When IGF-1 was introduced in the regression model as quartiles, the superior quartile was negatively associated with gain in height at 2 years (beta -0.361, P 0.043). SDS height gain at 6 months (beta 0.991, $P<0.0001$) and 1 year (beta 1.034, $P<0.0001$) of treatment were independently associated with SDS height gain at 2 years after adjustment for confounders.
Conclusion
Short children with highest IGF-1 SDS at diagnosis might have lower response to somatropin administration irrespective of GH reserve. However, the early response to somatropin administration independently predict the 2 year response to treatment, being a possible tool for guiding the therapeutic decision.

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EP689

Clinical experience of single tertiary center in managing patients with paraganglioma

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Paragangliomas (PGLs) and pheochromocytomas (PCCs) are rare neuroendocrine tumors that arise from chromaffin cells of the adrenal medulla and the

sympathetic/parasympathetic neural ganglia, respectively. We retrospectively analyzed 82 patients (43 female and 38 males) predominantly with PGLs who were hospitalized between January 2002 and December 2022. Twenty one patients were lost to follow up. The median age at diagnosis was 47 years (11–75) and the mean tumor size was 52.5 mm (26–170 mm). PGLs in our group were mostly distributed in abdomen (57%), head and neck (24.5%), rarely in spine (8.2%) and chest (3.2%). Four of our patients had coexistence of PCC. Hereditary form of disease was present in 19.5% of patients. The most common mutation was in SDHB gene (10/16), hereafter in VHL gene (3/16); 2 patients had mutation in SDHD gene and one in SDHC. Multiple PGLs at diagnosis were identified in 8 patients. Hormonally secreting tumors were present in 32% and 51% of patients had hypertension. Patients were treated mostly with surgery (86%) and tumor embolization (11.6%) in case of head and neck PGLs. At 30 patients, the median proliferation index Ki67 was 2.25% (0.1–25%). Median PASS score was 5 (1–14). Relapse of disease was present in 17% of patients with mean time to relapse 26 month (0–168). Metastatic disease was present in 18.8% of patients at the time of diagnosis and 6 patients had acquired metastasis. Mean time between initial and malignancy diagnosis was 28 months (range 0–300). These patients were treated mostly with PRRT (6/17), chemotherapy (4/17) and sutent (3/17). Median overall survival (OS) was 339 months (95%CI 305–373) with 10-year OS 93%.

We presented clinical characteristics, genetic profile, treatment options and survival of patients with PGLs, our experience as single tertiary center.

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EP690

The role of peptide receptor radionuclide therapy in a case series of bronchial and gastroentero-pancreatic neuroendocrine tumors with secondary determinations

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Introduction

Neuroendocrine tumors (NET) represent a heterogeneous group of tumors with different locations, whose management is based on the pathology, immunohistochemical, genetic and molecular profile.

Materials and method

We followed 8 patients with NET between 2014 and 2022 registered at the "C.I. Parhon" National Institute of Endocrinology, Bucharest, who benefited from peptide receptor radionuclide therapy (PRRT). Among them, 75% were male with the average age at diagnosis 43.37 ± 7.15 years. According to the WHO 2019 classification, 1 case presented a well-differentiated tumor grade G1, 5 cases G2, 1 case associated 2 tumors with grade G1 + G2 and 1 case pancreatic mixed neuroendocrine–nonneuroendocrine neoplasms (MiNEN).

Results

The primary localization was in 6 cases pancreatic, one bronchial and pancreatic, one ileo-cecal. All patients presented secondary determinations at diagnosis, 50% hepatic, 42% lymphnodal and 8% vertebral. Sporadic forms were in 6/8 cases and 2/8 cases presented MEN1 syndrome, in one case having confirmed the heterozygous deletion of the MEN1 gene (c.928-33_963del). At diagnosis, carcinoid syndrome was present in 6/8 cases and the average of chromogranin values in 5/8 cases being 1236.4 ± 881.2 ng/ml. In 3 patients, the presence of somatostatin receptors was evaluated: SSTR2 positive, moderate expression in 2/3, respectively strong expression in 1/3, and SSTR5 negative in 1/3, positive with weak expression in 1/3 and moderate expression in 1/3 cases. Six cases presented progressive disease before the initiation of PRRT treatment and the average interval from diagnosis to PRRT was 16.62 ± 14.27 months. The patients performed between 2 and 6 cycles with an average of 3.37 cycles, the radionuclides used was: (177)Lu-DOTATOC (average cumulative dose(ACD) = 16.5 GBq), (90)Y-DOTATOC (ACD = 10.57 GBq) and (225) Ac-DOTATOC (ACD = 20.5 MBq). The treatment associated with PRRT was: somatostatin analogs (87.5%), surgery (75%), chemotherapy (25%), chemoembolization (12.5%). PRRT was never used as the first line of treatment. Regarding the evolution of the disease according to the RECIST1.1 criteria determined over a period of 6 months after the end of the treatment, 50% presented a partial response, 37.5% stable disease, respectively 12.5% (1 case) progressive disease, the case being represented by the tumor MiNEN, where the death also occurred. Neuroendocrine tumor marker Cromogranine A decreased from the average of 1236.4 ± 881.2 ng/ml before PRRT, at 200.2 ± 188.4 ng/ml, at approximately 4.8 months after the last PRRT session.

Conclusions

PRRT shows benefits in the case of well-differentiated neuroendocrine tumors grade G1-G2, with bronchial or gastroenteropancreatic localization, and remains controversial in the case of poorly differentiated tumors, respectively MiNEN.

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EP691

A systematic review of pituitary apoplexy and Takotsubo cardiomyopathy

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Introduction

Pituitary apoplexy is defined as a clinical syndrome resulting from sudden hemorrhage or infarction of the pituitary gland, mostly within a pituitary micro/macroadenoma. One of the rare diseases that has been reported following pituitary apoplexy is Takotsubo cardiomyopathy (TC). TC, also known as stress cardiomyopathy, is a transient left ventricular dysfunction in the absence of coronary artery disease that is usually associated with psychological and physiological stressors. The purpose of this study was to systematically review the papers describing patients with TC and pituitary apoplexy.

Methods

This study is a systematic review that followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed, Web of Science, Scopus, ScienceDirect, and Google Scholar were searched up to 2022 using the following keywords: "pituitary apoplexy", "pituitary hemorrhage", "pituitary infarction", "Takotsubo cardiomyopathy", "Takotsubo syndrome", "stress cardiomyopathy", and "broken heart syndrome". English studies reporting TC in patients with pituitary apoplexy were included without any age, gender, and nationality restrictions.

Results

A total of 6 studies describing 6 cases, including 2 (33%) males and 4 (67%) females, were included. The age range of the patients was from 62 to 85 years with an average of 74 years. In past medical history, atrial fibrillation, complete heart block, hypertension, mild cognitive impairment, diabetes insipidus, nausea, and vomiting were reported. The most common signs and symptoms included altered level of consciousness (6 patients, 100%), headache (5 patients, 83%), nausea/vomiting (4 patients, 67%), hypotension, tachycardia, fever (each one: 3 patients, 50%), and neuro-ophthalmic diseases (2 patients, 33%). The electrocardiogram revealed T wave inversion in limb and/or precordial leads in all patients. Echocardiography showed left ventricular ballooning, apex akinesia, and left ventricular ejection fraction reduction with the lowest level of 20%. In laboratory data, ACTH/cortisol insufficiency (6 patients, 100%), abnormal thyroid function test (5 patients, 83%), low testosterone (3 patients, 50%), and elevated troponin were reported. All patients had pituitary adenoma, of which 4 (67%) were treated conservatively and 2 (33%) with transsphenoidal surgery.

Conclusions

It seems that TC can be a rare complication of pituitary apoplexy. The exact mechanism is not understood, but it may be related to endocrinological abnormalities including ACTH, cortisol, and thyroid hormones insufficiency. So, in case of suspicion of TC associated with pituitary apoplexy, it is recommended to perform more appropriate paraclinical measures such as troponin test, electrocardiography, and echocardiography to prevent misdiagnosis and mismanagement.

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EP692

Macrohormones ("incidental hormones") – a diagnostic challenge in endocrinology: macro-ACTH

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Background
If the laboratory results are not compatible with the patient's clinical symptoms, the presence of possible test interference should be considered. Despite the excellent quality of immunoassays, it is currently estimated that they may be susceptible to several types of interference that may lead to patient misdiagnosis.
Case report
In our case report we present a 71-year-old woman with confirmation of macro-adrenocorticotropic hormone (macro-ACTH). A magnetic resonance imaging (MR) scan revealed macroadenoma of the pituitary gland (size 16×12×14 mm). Laboratory tests revealed repeatedly high plasmatic levels of adrenocorticotropic hormone (without clinical manifestation of hypercortisolism or hypocortisolism), normal plasma cortisol levels with circulating variation and normal 24 – urine free cortisol. Plasmatic levels of another pituitary hormones were normal. A 2 mg and 8 mg dexamethasone blockade were performed with adequate cortisol suppression. Short synacthen test excluded adrenal insufficiency. Due to the suspicion of the presence of interference, we performed precipitation with polyethylene glycol (PEG-precipitation), which confirmed the high probability of the presence of macro-ACTH.
Conclusion
Although the presence of macrohormones is rare, some cases appear in clinical practice, which must be resolved through differential diagnosis. Systematic search for these interferences in clinical practice is not recommended, but an active approach to interference detection can prevent patient misdiagnosis. In our patient, despite the confirmed diagnosis of macro-ACTH, the transsphenoidal resection was performed. Histopathologic and immunohistochemical findings revealed non-functioning pituitary adenoma.

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EP693

New point mutation in the KAL 2 gene

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Although we know the gene alterations associated with KAL 2, at present we still do not know certain mutations of the fibroblast factor receptor 1 gene (FGFR gene) that even show complete penetrance of the syndrome. Kallman syndrome is a genetic disease of embryonic development characterized by the association of hypogonadotropic hypogonadism due to GnRH hormone deficiency because of agenesis or hypoplasia of the olfactory sulci. Three subtypes have been described; the classic or KAL1 linked to the X chromosome. The autosomal dominant form, KAL2, with the associated gene FGFR located at 8p11.2-p11.1, and the Kallman syndrome type 3 (KAL3). In this context, we present the case of a 14-year-old male patient who came to our clinic due to hypogonadism to affiliate. His personal history includes normal pregnancy, congenital right cryptorchidism diagnosed at 3 years of age, and anosmia from second childhood. In the directed anamnesis, no family history of interest with the diagnosis was found. At the time of the examination, he presented axilarchy. G1P sexual development, classified as grade II on the Tanner scale. Testicular volume of 1/2cc located in the inguinal canal. A Kallman-like Syndrome was suspected as the probable cause of the condition, and testicular ultrasound and cranial MRI were requested to complete the study. The testicular ultrasound described small-sized testicles for his age located in the most proximal part of the scrotal sac, impressing the horizontalized right testicle. In the cranial MRI, as pathological findings, an absence of the olfactory bulb and signs of hypoplasia of the olfactory grooves were observed, as well as a decreased adenohypophyseal gland in size. The analytical study with hormonal profile showed values of hypogonadism with decreased values of gonadal-stimulating hormones: FSH 0.3, LH 0.3, estradiol 5. Rest of hormonal profile was normal. A genetic study was requested to confirm the suspected diagnosis of Kallman Syndrome, being detected as a heterozygous carrier of c.983T>C (p.L3285) in the FGFR1 gene, which is associated with Kallman Syndrome type 2. The karyotype study did not show abnormalities. After genetic confirmation, treatment with intramuscular testosterone and evaluation of evolution in successive reviews was decided. With this case we confirm a new identifiable genetic finding for Kallman Syndrome type 2, this being the first report of said mutation related to idiopathic hypogonadotropic hypogonadism. The fact that the patient has no family history makes us think of a probable spontaneous mutation with complete syndrome penetrance.

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EP694

Thyrotropin-secreting pituitary tumor: a rare entity

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TSH-secreting pituitary adenomas are a rare cause of hyperthyroidism. The diagnosis should be considered in all hyperthyroid patients, especially those with a diffuse goiter and no extrathyroidal manifestations of Graves' disease. Most TSH-secreting adenomas secrete only TSH. Most patients have the typical symptoms and signs ofhyperthyroidism (eg, palpitations, tremor, heat intolerance), but a few patients have mild or even no hyperthyroid symptoms. Other clinical features include a diffusegoiter, visual field deficits, headache, and, in women, menstrual disturbances and galactorrhea. Thyroid function tests shows normal or high serum TSHconcentrations and high serum total and free thyroxine (T4) and triiodothyronine (T3)concentrations. Approximately 50 to 85 percent of patients with TSH-secreting pituitaryadenomas (particularly macroadenomas) have a high serum concentration of the alphasubunit of glycoprotein hormones. The differential diagnosis should be done with assay interference and resistence to thyroid hormone. The initial treatment of a TSH-secreting pituitary adenoma is medical therapy (withsomatostatin analogs) to restore euthyroidism prior to surgery. Once euthyroid,transsphenoidal resection of the tumor is the most appropriate definitive therapy forpatients with TSH-secreting pituitary adenomas. Here I present the case of a 43-year-old woman, referred by her Primary Care physician due to an incidental analytical finding of hyperprolactinemia. The patient was clinically asymptomatic, without symptoms derived from pituitary hyper or hypofunction, nor compression symptoms. The initial study revealed a 12 mm pituitary adenoma on MRI. The pituitary function study revealed slightly elevated T4 levels, with TSH in the normal range and an elevated alpha subunit. There was doubt between a non-functioning or a TSH-producing adenoma. Therefore, a new determination of thyroid hormones was obtained in another laboratory, with the same result; thyroid autoimmunity, which was negative, and a genetic study was subsequently performed, which ruled out resistance to thyroid hormones. The patient did not tolerate the TRH test. After one year of treatment with somatostatin analogues, TSH and T4 levels have been normalized, as well as the tumor has shrunk. Clinically, the patient remains asymptomatic, visual campimetry is normal, and she has not noticed adverse effects derived from medical treatment. In this case we see the difficulty of diagnosis, given the infrequency of the entity and the absence of florid symptoms, as well as the efficacy of treatment with somatostatin analogues, both in terms of normalization of thyroid function and reduction of tumor size.

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EP695

Anti PD1 induced hypophysitis: a different nosological entity?

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Introduction
The indications for anti-PD1 agents have expanded considerably in recent years, particularly for the treatment of melanoma, lung cancer and kidney cancer.
Hypophysitis is a rare complication of anti-PD1 agents (< 1%) often with an atypical presentation, characterized by a later onset and a less symptomatic presentation.
Case report
A 60-year-old woman was diagnosed with a clear cell renal carcinoma, treated with left nephrectomy in 2018. Two years later, peritoneal, ovarian and hepatic secondary lesions of the cancer have been identified. Checkpoint inhibitors immunotherapy was initiated using NIVOLUMAB (anti-PD1) and IPILIMUMAB (anti-CTLA4). Pre-therapeutic thyroid and pituitary workup did not reveal any abnormality. Between the 2nd and 3rd cure the patient developed a

thyroiditis with initial hyperthyroidism followed by hypothyroidism. Anti-TSH receptor and anti-thyroperoxydase antibodies were negative. Replacement therapy with LEVOTHYROXINE was introduced. IPILIMUMAB was interrupted and NIVILUMAB was majorated by the oncologist. Unfortunately, no systematic monitoring of the pituitary hormone workup was completed between the different treatment cures. During the following months, the patient complained of severe fatigue and nausea with a tendency to lose weight but with otherwise a normal clinical examination. Hormonal assessment confirmed an isolated corticotropic insufficiency with extremely low cortisol level and undetectable ACTH. The rest of the pituitary hormones were in the normal range, with elevated FSH in relation with menopause and normal prolactin. Pituitary MRI showed no abnormalities. HYDROCORTISONE substitutive treatment rapidly resumed all symptoms.

Conclusion

Hypophysitis induced by anti-PD1 seems to be a different nosological entity. Corticotropic insufficiency is often isolated and the symptoms are not very pronounced, apart from fatigue and weight loss which can be attributed to the cancer and/or the treatment regimen used. Through this case, we want to emphasize the importance of hormonal screening before initiating immunotherapy but also regularly during the treatment in order not to miss the diagnosis of a potentially life-threatening pathology.

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EP696

Clinical case of reverse hearing loss in a patient with acromegaly and pituitary macroadenoma

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Background

Acromegaly is an orphan neuroendocrine disease characterized by a variety of complications. Due to slow symptom progression acromegalic patients often are involved in growth hormone complications correction for a long time instead of search for main cause of these multiple disorders. A view on conductive hearing loss in acromegaly in literature is contradictory. The low incidence of hearing in acromegaly, compared with other complications, is presumably due to the topographic and anatomical location of the pituitary tumor.

Case presentation.

Female patient, 29 years old, was hospitalized in an endocrinological hospital in 2022 with suspected active stage of acromegaly and pituitary adenoma measuring 57×35×32 mm with endo-supra-infra-ante-latero(D+S) sellar growth, chiasm compression (greater on the left), with tumor expansion into in the main sinus and cells of the ethmoid labyrinth, as well as in the cavernous sinuses, more in the left. According to the hormonal study, IGF-1 was 645.2 ng/ml (normal to 311) and growth hormone more than 80 ng/ml (up to 6.9) , which confirmed the hormonal activity of the adenoma. The patient complained of a significant hearing loss and was consulted by an otolaryngologist. Based on the conducted audiometry, chronic bilateral sensorineural hearing loss III degree on the right and I degree on the left, as well as a bilateral increase in the perception thresholds of the III degree on the right and I degree on the left, was diagnosed. Because of transnasal transsphenoidal adenomectomy was performed. According to the results of immunohistochemical study – sparsely granulated somatotropinoma. After surgical treatment, the patient noted an improvement in hearing, repeated audiometry confirmed the positive dynamics of auditory function – a diagnosis of minimal bilateral chronic conductive hearing loss of the 1st degree was established. Such dynamics confirmed the genesis of hearing impairment as a result of hypertrophy of the temporal bone, due to hyperproduction of growth hormone, with subsequent damage to the auditory analyzer of the inner ear.

Conclusions

This clinical case shows the presence of conductive hearing loss in acromegaly and its reversibility after surgical treatment. Allied physicians should be aware of the variety of symptoms and complications of acromegaly, pay attention not only to the main reason for contacting a specialist, but also to the appearance of the patient, accompanying complaints.

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EP697

Prolactinoma's resistance: diagnostic and treatment perspectives via pharmacokinetic and metabolomic characteristics

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Introduction

Prolactinomas are the most common type of pituitary adenomas(40% of them) , representing a significant cause of infertility and hypogonadism. About 20% of patients with prolactinomas don't respond satisfactory(i.e. resistant) even to high dose dopamine agonist(DA) treatment(>3.5–4.5 mg/week). Worth noticing that there are no clear signs to anticipate this resistance but to stepwise increase the dose of DA. In addition, the etiology of resistance – subject of lively discussions.

Aim

The aim of our study was to assess metabolism and absorption of cabergoline in patients with DA-resistant prolactinomas.

Materials and methods

In patients($n=7$) with resistant prolactinomas (no normalization of PRL, no menses with max tolerated dose of cabergoline more than 3.5 mg a week) and 7 patients with normal effect of the drug we conducted a specific pharmacokinetic test: 1) cabergoline was preliminary withdrawn 4 days before the test; 2) at 0900 the blood was taken before and 30-, 60-, 90-, 120-minutes, 4 h, 8 h, 24 hours after taking the cabergoline in a fixed doze of 0.5 mg. The concentration of cabergoline substance in the serum was measured using high-performance liquid chromatography–mass spectrometry method(LC–MS/MS).

Results

We found significant differences in serum cabergoline concentration specific to patients with DA-resistant prolactinomas. It is shown that cabergoline concentration curve in patients with resistance to treatment doesn't represent expected pharmacokinetic peaks(the growth rate less than +1–50%). The pharmacokinetic curve of 1 resistant patient represented the peak at 30 min point(the growth rate +175%) with subsequent decline to baseline levels. The cabergoline concentration curve of drug-sensitive patient is characterized by an already significant baseline concentration that becomes progressively higher reaching an outstanding peak(the growth rate +112%) at the end of the test period. Differences in cabergoline concentration persist between two groups of patients over time, reaching a maximum by the 120th and 240th minutes. The values of these time points can be used as cut-off for differentiation the etiologies of drug resistance in prolactinomas.

Conclusion

Our pilot results show that the patients with DA-resistant prolactinomas may have a defect(absorption or metabolic abnormalities) in forming an adequate blood concentrations of the drug as well as genetic or receptors alterations. Understanding the underlying mechanisms will allow us to reveal treatment's resistance at the early diagnostic stage and develop personalized treatment strategy. In vivo pharmacokinetic and metabolomic characteristics of cabergoline can identify a number of causes of resistance to therapy, which has major clinical applications.

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EP698

Are neurosteroids related to anxiety and quality of life in cases with acromegaly?

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Background

Anxiety level is higher in the samples consisting of people diagnosed with pituitary adenoma, including patients with acromegaly, compared to the normal population. A higher level of anxiety indicates a lower Quality of Life (QoL) in acromegaly. This study aimed to evaluate and discuss the possible relationship between anxiety and NS in people with acromegaly.

Method
This cross-sectional comparative study included an acromegaly group (AG, $n=33$) and cases group without acromegaly (CG, $n=30$). People with a history of stroke with a current or past diagnosis of any psychiatric disorder or on steroid therapy were excluded. The data were collected with a Demographic Data Form, Beck Anxiety Inventory (BAI), Short Form (SF-36), SF-36 has subscales as general health, physical functioning, role limitations due to physical health, energy/fatigue, emotional well-being, social functioning, and pain. Also, levels of allopregnanolone (AP), pregnenolone (PRG), 24S-hydroxycholesterol (24OHC), dehydro-epiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS) and androsterone (ADT) as neurosteroids (NS) are measured in this study.
Results
There were statistically significant differences between the AG and the CG for BAI, general health, physical functioning, role limitations due to physical health, energy/fatigue, social functioning, and pain by the Mann–Whitney U test ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P = 0.017$, $P < 0.001$, $P < 0.001$). There was a statistically significant difference between the acromegaly and the control groups for DHEA (Median of AG:6.37, Median of CG:9.48) and 24OHC (Median of AG:8.70, Median of CG:44.25) by the Mann–Whitney U test ($P = 0.007$, $P = 0.002$). There are relationships between emotional well-being and 24OHC, between energy/fatigue and DHEA, and between energy/fatigue and DHEAS ($r = 0.39$, $P = 0.044$; $r = 0.465$, $P = 0.014$; $r = 0.443$, $P = 0.021$) in AG. There are relationships between BAI and general health, energy/fatigue, emotional well-being, social functioning ($r = 0.455$, $P = 0.008$; $r = 0.442$, $P = 0.01$; $r = 0.412$, $P = 0.017$; $r = 0.456$, $P = 0.008$) in AG.
Conclusion
Variation may occur in levels of anxiety and QoL in acromegaly. Levels of neurosteroids may contribute to it for people with acromegaly. Further research, about functions of neurosteroids may contribute to identifying possible pathophysiological processes.

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EP699

Pathologic characteristics of somatotroph pituitary tumors – an observational single-center study

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Background
The first-line treatment in acromegaly is transsphenoidal adenomectomy of GH-secreting pituitary tumor. Pathologic evaluation of postoperative tissue is an essential part of patient's assessment.
Aim
The aim of this study was to analyse pathologic characteristics of pituitary tumors in patients with acromegaly.
Patients and methods
One hundred twenty patients with acromegaly after at least one pituitary surgery treated in Endocrinology Department in Bielanski Hospital in Warsaw, Poland were included in this retrospective study. The data on demographics, hormonal, imaging and pathologic results were extracted from the Polish Acromegaly Registry. The study focused on comparison between sparsely (SG) and densely granulated (DG) tumors, GH(+), GH(+) PRL(+) and plurihormonal tumors, α-subunit (α-SU)-positive and α-SU-negative tumors and tumors of various Ki-67 index values in terms of above-mentioned characteristics.
Results
SG tumors occurred in 59 patients (55.66%) and DG tumors were diagnosed in 47 patients (44.34%). SG tumors compared to DG tumors were more frequent in women than in men (73.47% vs. 26.53%, $P=0.001$) and in younger patients [median = 39 years (IQR:32–49) vs. 46 years (IQR:38–58), $P=0.011$]. SG tumors were larger than DG tumors [23 (IQR:20–34) mm vs. 13 (IQR:9–20) mm, $P<0.001$].
Sixty-three tumors stained positive only for GH in immunohistochemistry (IHC) evaluation (53.39%), 46 tumors stained positive for GH and PRL (38.98%) and 9 tumors stained positive for at least three anterior pituitary hormones including GH (7.63%). Patients with GH(+)-PRL(+)-tumors presented with higher PRL concentration and more frequent gonadotropin insufficiency ($P=0.004$ and $P=0.022$, respectively).
Forty-nine tumors stained positive for α-SU (41.88%) and 62 tumors stained negative (52.99%). Tumors with α-SU(+) were smaller and were more often DG tumors compared to tumors with α-SU(−) [16.0 mm (IQR: 10–21) vs. 20.0 mm (IQR: 14–31), $P=0.013$ and 75.51% vs. 35.71%, $P<0.001$, respectively]. Tumors with α-SU(+) expanded extrasellarly less often than α-SU(−)-tumors (40.0% vs. 61.02%, $P=0.039$).
Proliferation index Ki-67 < 1% was found in 89 patients (76.72%) and Ki-67 ≧ 3% in 11 patients (9.48%). Patients with higher Ki-67 index were younger at diagnosis of acromegaly ($P<0.001$) and more often diagnosed with genetic syndromes ($P=0.02$), they had higher GH concentration ($P=0.007$), larger tumors ($P=0.006$) and cavernous sinuses invasion more frequently ($P=0.022$).
Conclusions
Pathologic assessment is an important part of acromegaly patients' evaluation. Pathologic characteristics are associated with patient's age, sex, hormonal results, tumor's size and degree of extrasellar expansion.

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EP700

Outcomes of Surgically treated Pituitary Adenomas in Malta – A Population-Based Study

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Aim
The sequelae of surgically treated pituitary adenomas (PAs) is an important area of study to help guide management. Our study aims to analyse all PAs, functional and non-functional, which were operated until the end of 2022 in a well-defined population and to identify radiological characteristics that can predict recurrence before operation.
Methods
206 PAs were evaluated along with their clinical, radiological, and histopathological characteristics. The clinical records of operated patients attending the only central national health service hospital in Malta were retrospectively analysed. Detailed clinical and histopathological data were obtained for each patient. The preoperative MR scan of each patient was analysed, and its radiological size, intensity patterns, suprasellar and infrasellar extension, and lateral extension were recorded. Univariate and multivariate analyses were done to establish the association of different variables and which variables can predict recurrence after operation.
Results
107 (51.9%) patients had a non-functional pituitary adenoma (NFPA), 20 (9.7%) had an ACTH-secreting PA, 68 (33%) had a GH-secreting PA, 10 (4.9%) had a prolactinoma and 1 (0.5%) had a TSH-secreting PA. The median age was 49 years (IQR 37–62). During the study period, 41 (19.9%) patients passed away. The subtype of PA was associated with MR T2 intensity patterns ($P = <0.001$). All prolactinomas, the TSH-secreting pituitary adenoma and 92.3% of NFPA were hyperintense while 80% of GH-secreting PA were hypointense. 41.7% of ACTH-secreting PAs were hyperintense, 33.3% were hypointense and 25% were isointense. 30 patients had tumour regrowth post-operatively, after a median of 39.5 months (IQR 19–84). Univariate analysis revealed a statistically significant association between tumour regrowth and the different subtypes of PAs ($P=0.02$), the presence of chiasmal compression ($P = <0.001$), suprasellar extension ($P=0.006$), cavernous sinus invasion ($P=0.001$), and the presence of residual tumour post–operatively ($P = <0.001$). Cavernous sinus invasion remained an independent predictor of regrowth after logistic regression ($P=0.006$; OR 6.5 95% CI 1.7–24.2). MR T2 solid tumour intensity was statistically significantly associated with maximal tumour diameter (P-value <0.001) and tumour volume (P-value < 0.001), with hyperintense tumours being the largest (median 26.9 mm; IQR 19.8–34.2), followed by isointense (median 14.3 mm; IQR 7.3–28.6) and hypointense tumours (median 11 mm; IQR 7.8–15.9). There was no statistically significant association between tumour regrowth and MR solid T2 intensity.
Conclusion
Our study shows that tumour size is strongly associated with baseline MR T2 intensity patterns. However, such patterns were not significantly associated with tumour regrowth occurrence, with other indices having a stronger association.

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EP701

Surgical treatment of prolactinomas

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It is known that treatment of prolactinomas with dopamine agonists is accompanied by relapses of the disease after discontinuation of the treatment in about 50% of cases and long-term or lifelong medication is required. The aim of the study was to evaluate the effectiveness of surgery in achieving remission or biochemical control of the disease. We prospectively enrolled 32 consecutive patients with prolactinomas who underwent transsphenoidal resection performed by the highly qualified surgeon. We evaluated the invasiveness of prolactinomas on the Knosp grading scale and measured serum prolactin concentrations on the first postoperative day. Routine histological assessment of the Ki-67 proliferation index was performed. The level of PRL was assessed in the early and in the late postoperative periods. Pituitary MRI with contrast enhancement was performed in 3, 6 and 12 months after surgery. Among 32 operated patients 32% achieved complete recovery and met the remission criteria during the entire follow-up period. In all patients who achieved remission, adenomas were noninvasive (Knosp 0, 1) and non-aggressive (Ki-67 $<3\%$). The average level of PRL on the first day after surgery was 295.2 mMEd/l ($P>0.1$). Biochemical control was achieved in 28%. In this group, 44% had noninvasive adenomas (Knosp 0, 1), 56% had invasive adenomas (Knosp 2,3). Ki-67 was $<3\%$ in all removed tumor tissues. The average value of PRL on the first day after surgery was 1244 mMEd/l. A significant reduction in the volume of prolactinomas after surgical resection (more than 80%) made it possible to normalize the level of PRL against the background of lower doses of cabergoline, compared with the doses of the drug taken before surgery. Patients who did not achieve postoperative remission and biochemical control accounted for 40% of the total number of patients. This group consisted of individuals with large (more than 4 cm) and giant (more than 6 cm) invasive tumors (Knosp 3,4). Ki-67 was $\geq 3\%$, which corresponded to a high degree of invasiveness and aggressiveness of the tumor. The average value of PRL on the first day after surgery in this group was 19 348 $\pm$ 7816 mMEd/l All patients had absolute indications for emergency surgery. Transnasal transsphenoidal adenomectomy leads to complete postoperative remission in 32% of cases and in 28% of cases allows to achieve biochemical control of the disease while taking cabergoline. Radiological assessment of prolactinoma invasiveness and early postoperative serum prolactin concentrations are important predictors of early remission after surgery.

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EP702

Pituitary apoplexy: clinical characteristics and management

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Background and aims
Pituitary apoplexy (PA) is a rare clinical syndrome due to pituitary hemorrhage or infarction. It is an emergent and potential life-threatening complication of pituitary adenomas if not managed properly. It is usually characterized by the sudden onset of one or more of the following: severe headache, visual disturbance, nausea/vomiting, and or altered mental status. We aimed to present clinical and biochemical characteristics as well as management of patients presented with pituitary apoplexy at our department.
Methods
In this study, a total of 14 patients presented with pituitary apoplexy between 2012 and 2022. The data of pituitary apoplexy cases were recorded. Resection rates, hormonal results, and clinical presentation of patients with pituitary apoplexy were evaluated.
Results
Over the last 10 years, 14 patients (2 women) were hospitalized for pituitary apoplexy. The median age of patients was 64.57 $\pm$ 16.11 years. Only one patient had a prolactinoma, the rest of them were non-functioning adenomas. Acute and severe headache was the most frequent symptom (100%), followed by visual disturbances 9/14 (64.3%) and diplopia 6/14 (42.9%). At presentation, the majority of patients 10/14 (71,42%) had one or more anteiror pituitary deficiencies. 3 of 14 tumors (21.4%) were causing cavernous sinus invasion. The median maximum diameter of the tumor was 28.2 $\pm$ 9.7 mm. Nine of fourteen patients (64,3%) underwent transsphenoidal surgery due to visual fields deffects or aggressive tumor.
Conclusion
Severe headache and visual disturbances are the commonest symptoms. Transsphenoidal surgery is the most frequent management.

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EP703

Silent pituitary macroadenomas – clinical behavior and prognosis

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Introduction
A third of pituitary adenomas are non-functioning. Classification depends on adenohypophyseal hormones expression and transcription factors.

Table 1 (Abstract EP703). Silent pituitary adenomas characteristics

	Gonadotropinomas								
	FSH/FSH + LH	FSH-/LH-SF1+	ACTH	TSH	PRL	FSH + LH + TSH	FSH + ACTH + PRL	GH + TSH	PRL + GH
Number	44 (67,7%)	5 (7,7%)	6 (9,2%)	2 (3,1%)	1 (1,5%)	4 (6,2%)	1 (1,5%)	1 (1,5%)	1 (1,5%)
Dimension (mm)	29,7 $\pm$ 7,1	30,7 $\pm$ 12,8	28,5 $\pm$ 6,9	27,5 $\pm$ 6,4	23	34,2 $\pm$ 6,8	41	24	37
Extension									
suprasellar	43	2	6	2	1	4	1	1	1
infrasellar	16	1	2	0	0	1	1	0	0
parasellar	29	1	6	0	1	4	1	1	1
Knosp									
0	1	1	0	0	0	0	0	0	0
1	7	1	1	1	0	1	1	1	0
2	22	1	4	1	1	0	0	0	0
3A	11	2	0	0	0	2	0	0	1
3B	1	0	1	0	0	1	0	0	0
4	2	0	0	0	0	0	0	0	0
Optic chiasm contact/compression	41	4	6	2	1	4	1	1	1
Sphenoid sinus invasion	5	0	0	1	0	0	0	0	0
Number of Surgeries	1,22 $\pm$ 0,6	1	2,3 $\pm$ 1,7	2	1	1,25 $\pm$ 0,5	2	1	1
Ki 67	$<3\%$ ($n=42$) 3–10% ($n=2$)	$<3\%$ ($n=5$)	$<3\%$ ($n=4$) 3–10% ($n=2$)[1]	$<3\%$ ($n=2$)	$<3\%$ ($n=1$)	$<3\%$ ($n=4$)	$<3\%$ ($n=1$)	$<3\%$ ($n=1$)	3–10% ($n=1$)
Cabergoline	5	2	0	0	1	0	0	0	1
Radiotheraoy	1	0	2	1	0	1	0	0	0

*In a silent corticotropinoma operated 5 times, Ki-67 increased in the successive histopathologic evaluations reaching 25%.

Aim
Characterize silent pituitary macroadenomas cases regarding their clinical data, treatment, histopathology and prognosis.
Methods
We revised clinical process of patients followed in CHULC. Cases with non-access to clinical follow-up registries or exams were excluded.
Results
Sixty-five patients (69.2% male), diagnosed at 53.6±14.3 years-old, followed during 6.6±4.4 years. 58.5% ($n=38$) were diagnosed in the context of tumoral mass effect; 21.5% ($n=14$) hypopituitarism; 9.2% ($n=6$) pituitary apoplexy and 10,8% ($n=7$) as an incidentaloma. 33,8% ($n=22$) had visual fields alterations with bitemporal hemianopsia being the commonest (9%; $n=16$). The characteristics of the different cases are summarized in Table 1 .
Conclusion
As expected, silent gonadotropinomas were the most prevalent and all the hormone negative adenomas expressed SF1. Although most of silent adenomas have a good prognosis, silent corticotropinomas seems to be more challenging to treat. Histopathology is decisive to predict the prognosis.

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EP704

Pituitary abscess masquerading as meningitis with partial anterior pituitary deficiency

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A 34-year-old woman presented with a worsening headache 4 weeks post-partum following emergency caesarean section. She described the headache as the worst that she had experienced, and this was made worse by bending forwards and with associated photophobia. A CT head scan revealed pan sinusitis and a suggestion of a pituitary tumour while lab results showed mild hyponatremia along with low TSH and FT4. An initial working diagnosis of likely meningitis was made, and she commenced on ceftriaxone and acyclovir. A LP was carried out which revealed xanthochromia and raised CSF protein while the CSF cell count revealed 324 cells with 70% lymphocytes and 30%neutrophils. A visual field testing showed no visual deficit. A baseline pituitary hormone profile showed elevated prolactin and normal cortisol and IGF-1 and she continued to become more hyponatraemic with a sodium of 117 mmol/l. The patient was commenced on levothyroxine as it was thought that the hyponatremia was the result of secondary hypothyroidism. An MRI pituitary revealed possible cystic macroadenoma or pituitary abscess. She was discussed at the pituitary MDT and advised to undergo a further MRI pituitary with diffusion weighted imaging as it felt the pituitary lesion was an abscess. She received a intravenous broad spectrum antibiotics while in the hospital though her inflammatory markers continued to remain normal. A repeat LP was carried out which showed the CSF cell count to be only 20 with 95%lymphocytes and the CSF protein had dropped. A workup for other infectious conditions including screening for HIV, TB, Hepatitis B, Hepatitis C and cryptococcus were all negative. The patient developed a recurrence of her headache post discharge with increasing tiredness and fatigue. A short synacthen test now showed central adrenal insufficiency while MRI pituitary suggested a likely pituitary abscess which was now multi septate with further progression to encroach on the optic chiasm with compression. She commenced steroid replacement and underwent a transsphenoidal drainage of the sellar abscess with frank pus noted intra operatively but no organism was isolated. She had an extended course of intravenous antibiotics over 4 weeks due to the nature of the pituitary lesion and had uneventful post operative recovery with improvement in her hyponatremia which had now normalized. This case highlights the rarity of the pituitary abscess and its close mimic to meningitis. The importance of recognising the need for prompt endocrine work up alongside other causes cannot be over emphasised.

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EP705

Pituitary macroadenoma apoplexy following treatment with pembrolizumab

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A 70-year old man was referred to the endocrinology department for the evaluation of a pituitary macroadenoma which was diagnosed during work-up for a malignant melanoma. Pituitary MRI showed a 20×21×25 mm adenoma with supra-sellar extension and no compression of the optic chiasma. Hormonal work-up revealed central hypogonadism and slight hyperprolactinemia due to stalk compression, while pituitary function was otherwise normal. MRI follow-up was scheduled in six months. The patient had surgery for the melanoma, and started immunotherapy with pembrolizumab. After the third dose of pembrolizumab, treatment was complicated by grade 3 polyarthralgia and grade 2 diarrhea and was temporarily stopped. Two-months later, the patient was admitted to the hospital due to violent headaches. MRI revealed apoplexy of the pituitary macroadenoma. Hormonal work-up showed new onset central hypothyroidism and central adrenal insufficiency. The patient was not on anticoagulation. Due to the absence of visual complications, conservative management was initially decided and treatment with glucocorticoids and levothyroxine was started. One week later, the patient came back to the hospital with worsening headache, motivating surgery. Histologic examination showed necrotic fragments of a pituitary neuroendocrine tumor, with SF-1 immunostaining. Possible metastasis of malignant melanoma was excluded. Central hypogonadism, adrenal insufficiency and central hypothyroidism persisted at 3 months-follow-up. Immune check-point inhibitors have radically improved cancer management. However, they are linked to endocrine adverse events related to pituitary, thyroid and adrenal damage. Pituitary complications include hypophysitis or simple anterior pituitary hormonal dysfunction. Pituitary apoplexy is an uncommon, potentially serious complication of pituitary macroadenomas. The pathophysiology is poorly understood, but some risk factors have been identified, such as coagulation disorders, abrupt increase or decrease in blood flow or pituitary stimulation. Here we describe the case of a patient who experienced apoplexy of a pituitary macroadenoma after pembrolizumab treatment. The link between immunotherapy and apoplexy has not been described so far. Only one case of apoplexy has been described in a patient on anti-PD1. With the increase in numbers of patients treated with immunotherapy, more research is needed to assess whether pituitary apoplexy can be caused by immune checkpoint inhibitors and determine whether pituitary surgery should be performed before starting immunotherapy.

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EP706

Translation into Portuguese and cultural adaptation of the Literacy Independent Cognitive Assessment

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Population aging has become a universal worldwide phenomenon. Developing countries (such as Portuguese-speaking countries, with a high rate of illiteracy) will see the greatest increase in the absolute number of elderly people, and dementia disorders will pose enormous challenges to public health in these countries. Although the decline in GH secretion with age has been associated with deleterious conditions of aging, our understanding is the opposite, that the decline in GH secretion attenuates the harmful consequences of aging (1), as shown in a cohort with a lifelong congenital, and untreated isolated growth hormone deficiency (IGHD), living in Itabaianinha, Brazil, the largest Portuguese-speaking country. These individuals exhibit normal lifespan and extended healthspan, that is, the period of life free of major chronic clinical diseases and disabilities, thus requiring an assessment of cognitive performance in the elderly. The aim of the present study was to translate and adapt a Portuguese version of the Independent Cognitive Literacy assessment (LICA). The study was carried out in five stages. In the first stage, a psychologist and a psychiatrist translated the instrument from English to Portuguese, maintaining the meaning and structure of the original version. This translation was proofread by an English teacher. The second step was the cultural adaptation, carried out in an interdisciplinary way by 15 authors, including a nutritionist who proposed common food terms in the interior of the Brazilian Northeast, generating the second consensus version after some changes of words and images, to become familiar in the local context. The third step involved an evaluation round with two judges (independent psychologists), who approved this version. In the

fourth stage, the instrument was revised by two senior authors, one psychiatrist and one endocrinologist, thus establishing the final Portuguese version of LICA. In the fifth stage, a pre-test was carried out to verify the understanding of the questionnaire, with five illiterates who understood and approved the instrument, which was later applied to 15 elderly people with isolated growth hormone deficiency and 15 local controls, in which we calculated the test score reliability, by Cronbach's alpha coefficient, based on all LICA standardized items, which was 0.76, indicating good instrument reliability. We conclude that the Portuguese version of the LICA is a reliable instrument, available to be used in this IGHD cohort, as well as in the cognitive assessment of any groups in internal medicine or psychology.

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EP707

Safety and efficacy of once weekly somapacitan versus once daily growth hormone among adults with growth hormone deficiency: A systematic review and meta-analysis

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Background

Adult growth hormone deficiency (AGHD) has been increasingly observed among patients with traumatic brain injury, stroke, and central nervous system infection, aside from the subgroup of patients with pituitary tumors. When left untreated, these patients have a significantly increased risk to develop cardiovascular morbidity and mortality and impaired psychosocial function. Existing treatment guidelines on AGHD have recommended the use of growth hormone (GH) replacement as the gold standard, of treatment, requiring daily GH injections, which can be burdensome and costly for patients. More recently, however, a novel drug Somapacitan (Novo Nordisk A/S, Denmark), was investigated in a number of small randomized controlled trials as an effective long-acting form of GH replacement therapy. It acts as a reversible albumin-binding GH derivative, thereby increasing its half-life and reducing its clearance from the body. Despite this discovery, on the other hand, there is no existing meta-analysis to create a more robust conclusion regarding its safety and efficacy.

Objective

This metaanalysis aims to evaluate the overall safety and efficacy of weekly somapacitan versus once daily growth hormone in adults with growth hormone deficiency (AGHD). Specific outcomes that were compared between weekly somapacitan and daily GH injections were the incidence of adverse effects, local tolerability, convenience scores of participants, and mean IGF-1 levels.

Methods

A comprehensive search of literature was done through electronic databases (Pubmed, MEDLINE, Cochrane Library) until December 1, 2022. The study included only phase 3 randomized controlled trials (RCTs) which were directed towards the adult population. RevMan 5.4 was utilized to analyze the efficacy and safety of weekly somapacitan versus daily growth hormone replacement.

Results and analysis

Three RCTs were included with a total of 415 participants. The incidence of adverse events including local injection-related reactions with weekly somapacitan as well as their mean IGF-1 levels were comparable to daily growth hormone injections but had better convenience scores, therefore increasing adherence to treatment which results to better quality of life.

Conclusion

Adherence to treatment plays an important role in improving treatment outcomes in patients with AGHD. With that, once weekly somapacitan can be offered as a safe and well-tolerated alternative to daily growth hormone injections among adults with growth hormone deficiency. This pilot meta-analysis was able to show the efficacy and safety of somapacitan versus the current standard, making it a promising treatment option to adults with growth hormone deficiency which can improve treatment compliance from childhood to adulthood.

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EP708

Giant pituitary adenomas: Clinical and paraclinical features, management, and outcome

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Introduction

Giant pituitary adenomas are defined as tumors with largest diameter $\geq$40 mm. They are characterized by high invasiveness causing compression of adjacent structures and hormonal dysfunction. The aim of this study was to determine the clinical and paraclinical features, management, and outcome of giant pituitary adenomas.

Methods

This was a single-center retrospective study including patients with giant pituitary adenoma. Clinical and paraclinical data were collected from the medical records.

Results

Twenty patients (14 men and 6 women) were included in this study. Their mean age at diagnosis was 34.8$\pm$11.9 years. Giant adenoma was revealed by a tumor syndrome in 17 patients and by signs of hypersecretion in two patients. It was incidentally discovered in one patient. The presenting manifestations were headaches (18 cases), visual disturbances (18 cases), hypogonadism (9 cases), signs of corticotrope deficiency (9 cases), and polyuria-polydipsia syndrome (1 case). The diagnosis of macroprolactinoma was established in 18 patients with a median baseline prolactin level of 8495 ng/ml. Two patients had non-secreting pituitary adenoma. Hypopituitarism was diagnosed in 9 patients. The mean adenoma size was 53.3$\pm$9.4 mm (range: 40–77 mm). Optic chiasm compression, cavernous sinus invasion, sphenoid sinus invasion, and hydrocephalus were observed in 14, 15, 11 and 10 patients, respectively. All patients with macroprolactinoma were treated with dopamine agonists (bromocriptine in 6 patients and cabergoline in 12 patients). Transsphenoidal surgery was performed to two patients and two patients required radiotherapy. Full recovery was obtained in only one patient. For the remaining patients, the outcome was marked by a decrease in the adenoma size in six patients.

Conclusion

Giant pituitary adenomas, although not very common, are a therapeutic challenge due to their size, invasiveness, and the fact that they often have extrasellar extensions.

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EP709

Long-term Clinical Outcomes in Acromegaly

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Background

Acromegaly is a rare condition characterised primarily by tumourous production of excess Growth Hormone (GH) from a pituitary adenoma. Clinical management aims at normalising serum IGF1 levels within sex and age-adjusted reference parameters. Treatment options include pituitary surgery, medical therapy with somatostatin analogue (SSA), cabergoline, pegvisomant or radiotherapy. A combination of treatment modalities is common for the majority of patients.

Aims

We retrospectively reviewed the long-term clinical outcomes in our large cohort of patients with acromegaly at the Royal Victoria Infirmary.

Methods

All patients with acromegaly seen in our dedicated weekly pituitary clinic or discussed in our pituitary MDT since 2019 were included. Data extracted: patient demographics, biochemical and radiological findings at diagnosis, treatment modalities, latest IGF1 level during follow-up and duration of follow-up. IGF1 expressed as x sex-and-age-adjusted upper limit of normal. Data expressed as mean, S.D. and percentages.

Results

From 1970 to 2021, 111 patients were diagnosed with acromegaly. F: M is 1:1, with a mean age of 48 ($\pm$16) years and IGF1 level 2.9$\times$ULN ($\pm$1.1) at diagnosis. 85% of patients had a pituitary macroadenoma. The mean duration of follow-up is 13 ($\pm$11.6) years. 75% of patients underwent pituitary surgery, and 24% were treated with medical therapy only. One patient is awaiting surgery. Overall 87/110 (79%) achieved an IGF1 $\leq$1.3$\times$ULN at the latest review. Post-pituitary surgery, 14% of patients achieved normal IGF1 levels, but 23% of patients achieved IGF1 $\leq$1.3$\times$ULN. Further treatment modalities to achieve IGF1 $\leq$1.3$\times$ULN in the surgical cohort included: cabergoline (10%), SSA (32%), a combination of SSA and cabergoline (8%), pegvisomant (4%) and radiotherapy (7%). Overall, satisfactory IGF1 control ($\leq$1.3$\times$ULN) was achieved in 50% of patients on SSA, 26% on cabergoline and 18% after radiotherapy.

Conclusions

The remission rate post-surgery in our cohort of patients with acromegaly, primarily secondary to macroadenomas, is low at 14%. Nevertheless, either alone

or in combination, long-term medical treatment modalities achieved adequate control in 79% of patients.

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EP710

Serum prolactin levels and correlation to clinical diagnosis: a study of 259 patients with hyperprolactinaemia

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Introduction
Hyperprolactinaemia is a common finding in endocrine practice and can be due to a number of causes. The degree of elevation of prolactin levels may sometimes be helpful in distinguishing between underlying aetiology.
Aim
To determine if hyperprolactinaemia is correlated with clinical diagnosis in a cohort of patients in the endocrine service at a tertiary centre.
Methods
A biochemistry database held at University Hospital of Wales, Cardiff, UK, was used to find patients who had prolactin levels requested by the endocrinology department between June 2019 and February 2022. This list was used to identify patients who had hyperprolactinaemia, as defined by serum prolactin levels of Males >407 mU/l and Females >557 mU/l, on at least two occasions. The initial elevated prolactin was noted and clinical records were examined to determine the clinical diagnosis made.
Results
A total of 1198 cases were identified. Out of these, 320 duplicates were removed, leaving 878 patients. 410/878 patients with hyperprolactinaemia were identified. 89 patients with incomplete data were excluded and 62 who only had a single elevated prolactin level measured were also excluded, leaving 259 patients. This cohort had their initial elevated prolactin levels identified between the years 2003 and 2022. 193 females and 66 males were identified. Mean age: 44 (17–91)y. A total of 10 diagnoses had been made, with mean prolactin levels and ranges as follows, in order of frequency of diagnosis: Microprolactinoma ($n=111$) 1797 (540–12 488)mU/l, macroprolactinoma ($n=40$) 26 776 (1330–160 452)mU/l, non-functioning pituitary adenoma (NFA) ($n=36$) 796 (466–1406)mU/l, Drug-Induced Hyperprolactinaemia (DIH) ($n=22$) 1989 (454–8355)mU/l, polycystic ovary syndrome ($n=15$) 1137 (628–2223)mU/l, idiopathic ($n=15$) 1113 (608–2458)mU/l, acromegaly ($n=8$) 3286 (444–17076)mU/l, stress ($n=6$) 866 (611–1261)mU/l, craniopharyngioma ($n=4$) 891 (595–1228)mU/l and empty sella ($n=2$) 1318 (1208–1427)mU/l. For the more common diagnoses, mean prolactin in microprolactinoma was higher than NFA ($P<0.001$), but there was no difference in mean prolactin in microprolactinoma compared to PCOS ($P=0.15$) or DIH ($P=0.64$). The mean prolactin in macroprolactinoma compared to NFA was statistically significantly higher ($P<0.001$), and also as compared to microprolactinoma ($P<0.001$).
Conclusions
A number of aetiologies result in elevated serum prolactin concentrations. Our data show hyperprolactinemia is more commonly found in females patients. Although there was an overlap in ranges between many of the diagnoses, in macroprolactinoma prolactin levels were no less than 1000 mU/l and in NFAs, no greater than 2000 mU/l. Mean serum prolactins were statistically higher in macro- and microprolactinomas compared to NFAs, and macroprolactinomas compared to microprolactinomas.

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EP711

Can early post-operative hypocortisolaemia predict remission after transsphenoidal surgery in Cushing's disease

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Background
Cushing's disease (CD) is rare, and standard treatment is trans-sphenoidal surgery (TSS). We previously reported a remission rate of 56% in patients undergoing TSS for CD from a microadenoma/normal pituitary on MR in our unit. Early post-operative hypocortisolaemia performs well at predicting durable remission early on. Post-operative day 1 cortisol of <55 nmol/l has a 100% sensitivity and <138 nmol/l 95% sensitivity at predicting remission. Since October 2021 all patients with CD are operated on by a single neurosurgeon in our unit and we have adopted early post-operative cortisol assessment.
Aims
We retrospectively reviewed the performance characteristics of early post-operative serum cortisol assessment in all patients undergoing TSS for Cushing's disease at our centre since October 2021.
Methods
Patients do not receive perioperative steroid cover during TSS for microadenoma or normal pituitary MRI and a 0600 h serum cortisol is checked on day 1 post-surgery before starting steroid replacement therapy. Subsequent hormonal assessment (short synacthen testing – SST) occurs 8–10 weeks post-operatively after steroid weaning and if euadrenalism is proven then dynamic testing for steroid excess is undertaken (dexamethasone suppression testing & 24-hour urinary free cortisol estimation).
Results
Nine patients with pituitary microadenoma and 2 patients with normal pituitary MRI underwent pituitary surgery for CD. F:M is 4:1. Day 1 post-operative serum cortisol level, measured in 10 patients, was <50 nmol/l, 50–150 nmol/l and >151 nmol/l for 6, 2 and 2 patients respectively. 10/11 (90%) patients remain in remission post-surgery. Eight patients failed their post-operative SST. Two out of three patients with normal SST post-operatively had normal steroid dynamics as assessed by dexamethasone suppression testing and 24-hour urinary free cortisol estimation. The one patient with ongoing CD did not have day 1 post-operative serum cortisol measurement.
Conclusions
Remission rate in Cushing's disease in patients with microadenoma or normal pituitary on MRI has improved to 90% in our unit. In our cohort day 1 post-operative serum cortisol level of >150 nmol/l did not predict persistent Cushing's disease as we observed late remission post TSS in 20% of our cohort.

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EP712

Thyroid fine needle aspiration for the diagnosis of Langerhans Cell Histiocytosis of the suprasellar region

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A 25-year old woman with Hashimoto thyroiditis was referred to the endocrinology department for investigation of a 40 kilogram weight gain, polyuria, polydipsia and secondary amenorrhea. Hormonal work-up showed diabetes insipidus, central hypogonadism, secondary adrenal insufficiency, central hypothyroidism and slight hyperprolactinemia. Pituitary magnetic resonance imaging (MRI) revealed a 15 mm hypothalamic tumor expanding to the infundibulum, associated with pituitary stalk thickening. Serum and cerebrospinal fluid tumor markers were negative and without evidence of infiltrative disease. Extensive whole body imaging was unremarkable except for high uptake of the suprasellar lesion (SUV 11.8) on 18F-fluorodeoxyglucose positron emission tomography and computed tomography (FDG-PET/CT). The patient refused transcranial biopsy for fear of potential complications. Due to mildly increased angiotensin-converting-enzyme and 24-hour urine calcium, neurosarcoidosis was suspected and prednisone was initiated (1 mg/kg) then stopped because of side effects (uncontrolled diabetes and weight gain) and the absence of radiologic improvement. Methotrexate was then prescribed and continued for a year. One year later, FDG-PET revealed high FDG uptake of the thyroid gland (SUV 4.1), which was also present at baseline and attributed to Hashimoto thyroiditis. Thyroid ultrasound showed heterogeneous pattern with slightly increased vascularity. On follow-up, thyroid parenchyma showed marked changes with intense hypoechoic pattern and decreased vascularity. Fine-needle aspiration (FNA) of the thyroid gland was then decided and cytology showed a proliferation of Langerhans cells with deeply grooved nuclei admixed with eosinophils. The Langerhans cells were strongly positive for CD1a by immunocytochemistry. Cladribin treatment was initiated and resulted in a significant decrease in tumor size within 2 months (craniocaudal axis on MRI: 19 mm versus 24 mm at baseline). Histiocytosis includes a group of syndromes characterized by tissue infiltration of histiocytes thought to be derived from dendritic cells or macrophages that may infiltrate various organs, notably the central nervous system. Thyroid involvement has rarely been reported, is more common in adults and is usually related to multi-systemic disease. Ultrasound

shows hypoechoic pattern, heterogeneity and rare calcifications. Thyroid FNA can be useful in establishing the primary diagnosis if no other tissue biopsy can be done and immunohistochemical staining shows positivity for S100, CD1a and langerin. Thyroid ultrasound should thus be performed in all patients with intracranial tumors suggesting LCH, especially in case of increased FDG-avidity of the thyroid parenchyma. FNA could be systematically considered as being part of the differential diagnosis workup in these cases.

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EP713

Kisspeptin Kindred: Case Report and Literature Review

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Context
Normosmic idiopathic hypogonadotropic hypogonadism (nIHH) is a rare endocrine disease in which patients have isolated gonadotropin releasing hormone (GnRH) deficiency in the context of otherwise normal structure and function of anterior pituitary and hypothalamus with normal olfactory ability.
Objective
To explore the underlying pathogenic defect in patients with delayed puberty.
Patients
We investigated genetic defects in a consanguineous family of Pakistan patients with nIHH. The proband is a male who presented with delayed puberty at the age of 22 years. His younger sister, who was 18 years old at the time of presentation experienced primary amenorrhea. Both of them have a normal sense of smell.
Methods
High-throughput exome sequencing with the NHS Genomic Medicine R148 Hypogonadotropic Hypogonadism gene panel (14 genes) was undertaken. The identified predicted pathogenic variant in *KISS1R* was confirmed by Sanger sequencing.
Results
Hormonal profiles confirmed isolated GnRH deficiency in the proband with undetectable LH and testosterone, and inhibin B 26.7 pg/ml, as well as in his younger sister. A homozygous variant in *KISSR1* was identified, namely a nonsense stopgain (c.827G > A; p.(Trp276Ter)) in both siblings. The variant is not present in the gnomAD database.
Conclusion
We describe a novel homozygous nonsense variant in *KISS1R* resulting in nIHH in one kindred exhibiting delayed or absent pubertal onset.
Keywords: hypogonadism, normosmic, delayed puberty.

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EP714

A patient with two forms of PA – pituitary adenoma and primary aldosteronism

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Background
Clinically relevant pituitary adenomas (Pit PA) affect approximately 1:1200 of the general population, and may manifest with hormone hypersecretion, hypopituitarism and compression of the visual pathways. Primary aldosteronism (Adr PA) is now recognised to account for 5–14% of all cases of hypertension and is associated with excess morbidity when compared with primary hypertension. Here, we report a patient who was noted to have a history suggestive of Adr PA whilst being investigated for Pit PA.
Case
A 45-year-old man attended his primary care physician with a 6-month history of reduced sexual function. Laboratory investigation demonstrated partial hypogonadotrophic hypogonadism [LH 2.6 U/l (RR 1.5–9.3); FSH 8.8 U/l (RR 1.4–18.1); total testosterone 6.7 nmol/l (RR 7.2–31.3)], with associated mild hyperprolactinaemia [prolactin 719 mU/l (RR 45–375)] and possible partial central hypothyroidism [Free T4 10.3 pmol/l (RR 10.5–21.0); TSH 0.7 mU/l (RR 0.35–5.5)]. Serum cortisol was normal with no evidence of Cushing's syndrome clinically or biochemically (UFC 42 nmol/24 h; LNSC 0.5 and 0.9 nmol/l) Serum calcium was normal. Formal visual field testing with perimetry showed a left temporal defect, and subsequent pituitary MRI revealed a 34 × 26 × 19 mm macroadenoma with suprasellar extension. Whilst being investigated for Pit PA, parallel investigations were initiated for suspected Adr PA based on the patient's history of hypertension (treated with amlodipine) and unprovoked hypokalaemia. Plasma renin concentration (PRC) was low (3 mU/l), which coupled with a plasma aldosterone concentration (PAC) of 790 pmol/l, yielded a markedly raised aldosterone: renin ratio (263.3). Adrenal MRI demonstrated a possible nodule in the body of the left adrenal gland, with thickening of the medial limb; the right adrenal appearances were unremarkable. Subsequent ACTH-stimulated adrenal vein sampling (AVS) indicated a bilateral origin of PA (Ttable 1): The patient was changed to mineralocorticoid receptor antagonist (MRA) therapy with good control of blood pressure and correction of hypokalaemia. At trans-sphenoidal surgery, a macroadenoma was resected, with immunohistochemistry showing positivity for FSH. Transcription factor expression is negative. Genetic screening for a familial syndrome is awaited.
Conclusions
Although, the co-occurrence of Pit PA and Adr PA in our patient may represent a simple coincidence, the possibility that they are linked [either through an underlying genetic predisposition (e.g., MEN1) or a novel pathophysiological pathway (as previously proposed for macroprolactinomas and Adr PA – Williams *et al*., JCEM, 2015)] remains.

	IVC	Left adrenal vein	Right adrenal vein
Aldosterone	1,160	44,200	32,500
Cortisol	1,037	17,585	14,114
A:C ratio	1.12	2.51	2.30

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EP715

Predictive factors of biochemical remission after transsphenoidal surgery in acromegaly

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Introduction
Excessive production of growth hormone (GH) in acromegaly is most commonly caused by a somatotroph pituitary adenoma. The therapeutic arsenal is based on selective transsphenoidal adenomectomy (STA) as a first-line treatment. The aim of our study was to determine predictive factors of postoperative biochemical remission in acromegalic patients.
Methods
We conducted a retrospective study including 18 acromegalic patients followed-up in the endocrinology department of Charles Nicolle hospital, who underwent STA. Clinical, biochemical, and tumor imaging data were extracted from medical records. According to postoperative biochemical investigation patients were subdivided into two groups: remission (normal IGF-1 and GH level < 1 ng/ml, 3 months postoperatively) versus persistence.
Results
There were 10 women and 8 men with a mean age of 42.9 ± 12.9 years. Pituitary imaging showed a macroadenoma in 94% of cases with extrasellar extension in 61% of cases. Postoperative biochemical remission was seen in six patients (33%). Patients who achieved biochemical remission had significantly smaller tumors compared with those who did not attain remission (mean diameter 15.2 versus 25.6 mm; $P = 0.018$). Moreover, locoregional invasion ($P = 0.043$) and the persistence of a tumor remnant ($P < 10\text{-}3$) were significantly associated with a decreased rate of biochemical remission. However, we did not find significant associations between postoperative biochemical remission and these parameters: age, sex, preoperative GH and IGF-1 levels, pituitary hormone deficiencies, visual impairment and the delay between the diagnosis of acromegaly and STA.
Conclusion
STA of somatotroph adenomas remains the only curative treatment in acromegaly. The biochemical remission rate obtained after STA ranges from 32 to 85% of cases. Consistent with literature, our study showed that postoperative biochemical remission rate is lower in case of voluminous adenomas, locoregional invasion and persistence of residual tumor.

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EP716

Coexistence of acromegaly and Xanthomatous Hypophysitis

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Introduction
Hypophysitis is a rare pituitary inflammation due to primary and secondary causes. Xanthomatous hypophysitis is the rarest subtype and described with lipid-laden cystic areas, transparent cytoplasmic and lipid-laden histiocytes and foamy (xanthomatous) histiocytes. Although the etiology of xanthomatous hypophysitis is not clearly known, it has been suggested to develop as a result of autoimmune cause or inflammatory process of infiltration of cyst components from other sellar masses. Clinically, it shows symptoms similar to pituitary adenomas, but no case of hypophysitis accompanied by acromegaly has been reported among the few cases seen in the literature. We present a case with xanthomatous hypophysitis which was diagnosed after re-operation for acromegaly.
Clinical case
A 38-year-old female patient presented with complaints of headache, enlargement of the hands and feet, increase in shoe size, and enlargement of the jaw for 6 months. Physical examination revealed acromegaly, other systemic examination was unremarkable. Laboratory examination revealed IGF1:659 ng/ml (93.1–228) and GH:24.4:4.02 ng/ml (0.126–9.88) Other anterior pituitary hormones were within reference ranges. MRI revealed a 19×13 mm hypointense mass lesion in the right lateral half of the pituitary. Visual field evaluation was normal. The patient was operated with a prediagnosis of acromegaly. The pathology result was compatible with acromegaly. 3rd month follow-up revealed IGF1:554 ng/ml (93.1–228) GH:8.79, ng/ml (0.126–9.88) other anterior pituitary panel was again normal and imaging showed a 12×12 mm residual mass in the right half of the pituitary. After re-operation for the residual tumor the pathology specimen of the second operative pathology was reported as sparsely granular somatotroph adenoma favoring focal recurrence/residue in the adjacent area containing CD 68+ diffuse foci of xanthomatous hypophysitis. Medical treatment for acromegaly was started.
Conclusion
Although the pathogenesis of xanthomatous hypophysitis is unknown, it may develop as a local reaction to hemorrhage, degeneration necrosis and inflammation. Also, it has been previously associated with rathke cleft cysts (lit). However, to our knowledge reoperation for a somatotropinoma has not been defined as a secondary cause. Immunohistochemical staining is supportive to confirm the diagnosis in our case.

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Bilateral petrosal sinus sampling – a 15-year experience from a tertiary hospital

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Introduction
In patients with ACTH-dependent Cushing Syndrome, differentiating between pituitary and ectopic sources can be challenging. Noninvasive testing can be performed, but bilateral inferior petrosal sinus sampling (BIPSS) remains the gold standard. In the last years however, novel imaging modalities, namely 3T-MRI with 3-dimensional spoiled gradient-echo sequence and 68Ga-tagged CRH combined with positron emission tomography, have been proposed as alternatives.
Aim
To evaluate the accuracy of BIPSS performed in a single tertiary hospital in differentiating between hypophyseal and ectopic causes of ACTH-dependent Cushing syndrome. A secondary aim was to compare BIPSS and traditional non-invasive test results (MRI, high-dose dexamethasone suppression test and CRH stimulation test).
Methods
Forty patients with ACTH-dependent Cushing syndrome underwent BIPSS from 2006 to 2022 in a tertiary hospital. Fourteen patients were excluded due to lack of documented hypercortisolism at the time of BIPSS, lack of a definitive diagnosis, or sample loss (hemolysis). Clinical files were reviewed for patient demographics, biochemical, histological and imaging findings. Cushing's disease was confirmed in case of cure after transsphenoidal surgery or histology indicative of an ACTH positive pituitary adenoma. Similarly, ectopic Cushing syndrome was confirmed in case of cure after surgery or histology indicative of ACTH-positive neuroendocrine tumor (surgery or biopsy).
Results
Twenty-six participants were evaluated (76.92% female, median age 43.31 ± 2.36 years). Cushing's disease was confirmed in 19 patients, and BIPSS was compatible with this diagnosis in 13 patients. Ectopic Cushing syndrome was confirmed in 5 patients, and BIPSS was compatible with this diagnosis in 4 patients. The fifth patient had results suggestive of ectopic Cushing syndrome before CRH stimulation, and Cushing's disease after. BIPSS sensitivity was 71.43%, and specificity was 100.00% and 80.00%, before and after CRH stimulation. Accounting for an estimated prevalence of Cushing's disease of 80% among patients with ACTH-dependent Cushing's syndrome, accuracy was 77.14% and 70.74%, before and after CRH stimulation. MRI ($n=26$) sensitivity was 66.67% and specificity was 60.00%. High dose dexamethasone suppression test ($n=14$) sensitivity was 80.00% and specificity was 25.00%. CRH stimulation test's ($n=8$) sensitivity was 100.0% and specificity was 0.00%.
Conclusion
BIPSS had overall lower sensitivity and higher specificity compared with non-invasive testing. Specificity was higher before CRH stimulation. Novel non-invasive diagnostic tools with higher accuracy in differentiating the cause of ACTH-dependent Cushing syndrome could possibly replace invasive testing in the future.

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EP718

Radiological characteristics of pituitary adenomas in men

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Background and aims
Pituitary adenomas (PA) are small, generally benign tumors found in the pituitary gland.PA in men are rare However, they are characterized by the frequency of invasive and aggressive tumours, which makes their management difficult. The aim of this study is to clarify radiological characteristics of pituitary adenomas in men. Materials and methods: Retrospective descriptive study of 80 adult men with PA, hospitalized in the endocrinology department from 1998 to 2020. It included 35 non-functioning adenomas (NFPA), 27 prolactin adenomas, 15 somatotropic adenomas and 3 corticotropic adenomas.
Results
The mean tumour size was 31.6 mm $\pm$17.2 [5–90 mm] with macroadenomas predominating; 55 cases (68.7%). Prolactinomas had the largest dimensions with a mean height of 46 mm [9–90 mm] compared to 27.8 ± 12 mm [9–56 mm] for NFPA, 27.6 mm $\pm$8.9 [9–56 mm] for somatotropic adenomas and 14.3 mm [5–37 mm] for corticotropic adenomas. Fifteen patients (18.7%) had a giant adenoma of which 13 patients had a prolactinoma. Macroadenomas were predominant in NFPA (88.5%), somatotropic adenomas (73.3%) and corticotropic adenomas (66.6%). Prolactin adenomas and NFPA were predominantly T2 hypersignal (71.1% and 74% respectively). Somatotropic adenomas, on the other hand, were predominantly T2-hyposignal (60%). Suprasellar extension was the most frequent, whatever the type of adenoma (59 cases, 73.7%), i.e. 82.8% of NFPAs, 85.2% of prolactinomas, 33.3% of somatotropic adenomas and 66.6% of corticotropic adenomas. Compression of the optic chiasma was found in 35% of cases and hydrocephalus in 15% of patients. The pituitary stem was compressed in 21.2% of cases. Lateral extension to the cavernous sinuses was found in 42.5% of cases, i.e. 66.6% of corticotropic adenomas, 45.7% of NFPA, 48.1% of prolactinomas and 20% of GH adenomas. Invasion of the sphenoidal sinus was noted in 16.2% of cases, all were giant adenomas. Posterior extension to the brainstem and prepontine cisterns was noted in 3 cases. The post-pituitary gland was pushed back in 2 cases. Finally, extension to the nasal cavity and orbit was noted in 3 cases. Radiological pituitary apoplexy was found in 38.7% of PA. A cystic component was present in 20% of NFPA and 30.7% of giant prolactinomas. Only one PA was abcessed. This was a NFPA.
Conclusion
PA are characterised by the frequency of macroadenomas and by a greater potential for progression. They are more prone to pituitary apoplexy, which causes higher morbidity and mortality.

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EP719

Polyuria after steroid replacement in a patient with adrenal insufficiency – not always vasopressin deficiency

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A 54-year-old man with a recurrent non-functioning pituitary gonadotroph adenoma previously treated with transphenoidal surgery (TSS) in 2015, presented to Charing Cross hospital for repeat transsphenoidal surgery in May 2022. Since his initial surgery, he remained on Levothyroxine 50 µg once daily only. There was no evidence of adrenal insufficiency (0900 h cortisol 333 nmol/l at day 6 following initial TSS). In February 2022, his electrolytes, FSH, LH, testosterone, prolactin and IGF-1 levels were normal. A repeat Short Synacthen Test (SST) showed normal results (baseline cortisol 94 nmol/l, 30 minutes 404 nmol/l, 60 minutes 451 nmol/l). Routine pre-operative bloods on the day of admission for repeat surgery in May 2022 showed a new hyponatraemia of 125 mmol/l (range 133–145 mmol/l) and an undetectable cortisol (<28 nmol/l). He was given an induction dose of Hydrocortisone pre-operatively, and immediately became polyuric passing over 200 ml per hour, with a total of 6050 ml in 24 h. His operation was postponed and the polyuria settled within 24 h. Repeat bloods the following morning showed a sodium of 133 mmol/l. He was discharged on replacement Prednisolone 4 mg once daily, and a repeat TSS was rearranged. The ACTH deficiency prevented free water clearance, which immediately reversed on treatment with Hydrocortisone. The ACTH deficiency was presumed to be a result of corticotroph suppression by tumour growth against the sella turcica. A subsequent water deprivation test on replacement Prednisolone, to ensure that the glucocorticoid replacement had not uncovered vasopressin deficiency, was entirely normal. He subsequently had TSS in June 2022. A postoperative SST revealed a baseline cortisol of 283 nmol/l, 30 min 517 nmol/l and 60 min 631 nmol/l. His Prednisolone was hence weaned down to 3 mg and then stopped. His TSH also normalized, and the Levothyroxine was stopped. Textbook definitions for syndrome of inappropriate antidiuretic hormone secretion (SIADH) state that patients must have adequate cortisol and thyroxine reserve to make the diagnosis. This case, however, confirms that deficiency of either, can present as SIADH, which resolves when these hormones are replaced. Our case also highlights that corticotrophs are sensitive to the pressure effects of pituitary tumours, but that full recovery can occur following surgical decompression. It is important that patients' hypothalamic–pituitary–adrenal axis are reassessed to avoid unnecessary glucocorticoid replacement.

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EP720

Increased mortality in COVID-19 patients with admission hyponatremia is associated with sustained hyponatremia, and volemia-inappropriate therapy

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Introduction
Admission hyponatremia, frequently detected in patients hospitalized for COVID-19, has been associated with increased mortality. However, although SIADH-induced euvolemic hyponatremia is the single most-common cause of hyponatremia in community-acquired pneumonia, repercussions of admission-hyponatremia volemic classification on COVID-19 hospitalizations have yet to be described. We sought to identify factors contributing to mortality and hospital length-of-stay (LOS) in hospitalized patients admitted with hyponatremia, taking volemia into account.
Method
Retrospective study of 247 patients admitted with COVID-19 to a tertiary hospital in Madrid, Spain from March 1st through March 30th, 2020, with a glycemia-corrected serum sodium level (SNa) < 135 mmol/l. SNa, creatinine, urea, glycemia, O2 Saturation were recorded at admission, at day 2nd–3rd of hospitalization, and ensuing days when hyponatremia persisted (>3 days). Volemia was determined according to: maximum height of internal jugular vein pulse (HIYP), and 2 of following: presence/absence of thirst, orthostatic symptoms, blood pressure ≤ 90/60 mmHg, heart rate ≥90 bpm, urinary sodium ≤ 30 mmol/l and/or a rise in serum creatinine (SC) and/or serum urea (SU) accompanying the descent in SNa. In absence of registered HIJP, 3 of the latter criteria were used. Variables studied included demographics, comorbidities, therapy of hyponatremia, LOS and in-hospital mortality rate.
Results
Age: 68 years [56–81]; 99/247 (39.9%) female. Median admission SNa: 133 mmol/l [131–134]. In the majority (188/247:76%), hyponatremia was mild (SNa 131–134 mmol/l). Volemia in 208/247 patients: 119/208 (57.2%) were euvolemic, and 89/208 (42,8%) were hypovolemic. The median LOS was 11 days [6–18], with a mortality rate of 21.5%. LOS was correlated with total hospitalization days with hyponatremia ($r=0.474$, $P<0.001$), and negatively correlated with admission SNa ($r=-0.224$, $P<0.001$). Patients who died had a higher median rate of hospitalization days with hyponatremia (25% vs. 17%, $P=0.007$) than survivors, with a shorter LOS: 7 [4–12] vs. 12 [7–20] days, $P<0.001$. Higher 02 saturation levels were independently associated with reduced mortality (OR: 0.88, 95%CI 0.78 to 0.99), and an oncological history with increased mortality (OR: 13.17, 95%CI 1.79 to 96.84). Neither the degree of hyponatremia, nor volemia were independently associated with mortality. However, initial therapy of hyponatremia was: euvolemic patients inadequately treated at admission with iv isotonic saline showed an increased mortality rate (36.6% vs 20.2% $P=0.02$).

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EP721

An international, simulated-use study assessing nurses' preferences between two lanreotide syringes (Somatuline Autogel vs Pharmathen) for treatment of neuroendocrine tumours (NETs) and/or acromegaly: PRESTO 3

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Introduction/Background
Patients with NETs and acromegaly are commonly treated with somatostatin analogues (SSAs), such as octreotide and lanreotide depot formulations. The Pharmathen syringe is now available in several European countries and the USA for lanreotide depot injection. When using SSAs, confidence in and ease of use with syringes is important for decision-making in long-term therapy.
Aims
PRESTO 3 compared nurses' preference for the Somatuline Autogel syringe versus the Pharmathen syringe after injection-pad testing. Here we report preferences for 11 attributes.
Methods
This international, simulated-use study included oncology/endocrinology nurses (initial planned sample size 92) with ≥1 year experience in managing NETs and/or acromegaly. Each nurse tested both syringes twice in a randomised order, before completing an electronic preference survey. The primary objective was to assess overall preference (%, 95% confidence interval [CI]) for the Somatuline Autogel syringe versus the Pharmathen syringe, assessed using a one-sample exact binomial test. Secondary objectives included ranking importance and rating performance (scored from 1 [not at all] to 5 [very much]; Wilcoxon 2-sided signed-rank test) of attributes for both syringes.
Results
Ninety-four nurses were enrolled: mean age, 41.0 (s.d., 11.5) years; 72.3% in Europe (7 countries) and 27.7% in the USA. The proportion of nurses stating a preference ('strong' or 'slight') for the Somatuline Autogel syringe [86.2% (95% CI 77.5%–92.4%)] was statistically significantly higher than 50% ($P<0.0001$). Ranking of syringe attributes are reported in the Table. Performance rating was statistically significantly higher with Somatuline Autogel than the Pharmathen syringe for 10/11 attributes ($P<0.05$) (Table 1).
Conclusions
This simulated-use study showed that nurses strongly preferred the user experience of the Somatuline Autogel syringe over the Pharmathen syringe. "Ease of use" and "comfortable to handle" were considered the most important

syringe attributes, and performance rating was significantly higher with Somatuline Autogel than the Pharmathen syringe for all but one attribute.

Attributes	Most important, %	Second most important, %	Least important, %
Easy to use	**30.9**	11.7	4.3
Comfortable to handle	20.2	**16.0**	1.1
Convenience of syringe format	8.5	11.7	9.6
Confidence that:			
• full volume is delivered	8.5	8.5	0.0
• a low-risk of needle-stick injuries	7.4	5.3	3.2
• a low-risk of syringe contamination	5.3	4.3	3.2
• no loss of product during preparation	5.3	5.3	3.2
• needle appears patient-friendly	2.1	4.3	22.3
Sturdy plunger during use	6.4	12.8	7.4
Easy to teach others how to use	3.2	8.5	19.1
Fast administration	2.1	11.7	**26.6**

Bold: most-, second-most and least-important attributes

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EP722

Experience with cabergoline in the treatment of an active gonadotropinoma

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Gonadotropinomas secreting biologically active hormones, most commonly follicle-stimulating hormone (FSH), are a very rare pathology. The clinical manifestations depend on the gender and age of the patient. Men may observe enlarged testicles and erectile dysfunction. Reports on the results of the drug treatment are sporadic.

Objective

To describe a rare clinical case of an active giant FSH-secreting pituitary tumour in a 62-year-old man with the development of hyperandrogenism and secondary erythrocytosis. Patient Y. 62 years old applied to the neurosurgical centre with complaints of decreased vision. MRI examination revealed a giant tumor of the chiasmal-sellar region (maximum size 63 mm). Ophthalmological examination: decreased visual acuity in the OS- 0.3, OD- 0.9, left-sided hemianopsia. ?ormonal tests: FSH – 30 U/l (1,4-9,6), LH – 8,6 U/l (2,5-11), testosterone – 58 nmol/l (12-27); PRL, TSH, free T4, IGF-1, cortisol levels were within the reference values. The clinical blood test revealed secondary erythrocytosis (Hb – 199 g/l (130–170), erythrocytes – 6.5×10.12/l, Ht – 58% (40–51)), other parameters were unchanged. Urological examination revealed moderate diffuse changes in the prostate gland, testicular volume was within the age norm. The somatic status had no features. The localization and size of the tumour determined a high surgical risk. The patient refused the proposed surgical treatment. Cabergoline therapy was attempted. A normalization of laboratory values was observed on a 1.5 mg weekly basis for 3 months (FSH – 10 U/l; LH – 2,7 U/l, testosterone – 9,5 nmol/l; Hb – 162 g/l (130–170), erythrocytes – 5.3×10.12/l, Ht – 46%. During the following 7 years of follow-up a control MRI of the brain with contrast (the interval of investigation was 3–6 months during the first 3 years, then annually) showed tumor without significant changes in its size. Visual function remained at the same level.

Conclusion

In this case, the increase in sex hormones did not lead to a recognizable clinical syndrome. It should be remembered that endogenous hyperandrogenism may be the cause of erythrocytosis. The lack of progression of neurological symptoms for 7 years and the normalization of laboratory values, as a demonstration of the tumor's "response" to therapy, allowed the patient to continue treatment with cabergoline. Further accumulation of clinical cases can determine the management for patients with active gonadotropinomas.

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EP723

Cure rates after different therapy lines among patients with growth hormone (GH)-secreting pituitary adenomas

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Introduction

Even Though resection via transsphenoidal surgery is the optimal primary treatment for growth hormone (GH) secreting pituitary adenomas, medical therapy must also be considered when biochemical control after surgery is not achieved. The aim of our study was to describe the cure rates of acromegaly patients after different lines of therapy.

Methods

A retrospective study (1971–2022) of 89 patients diagnosed with acromegaly was conducted. Age, sex, radiological characteristics of the pituitary adenoma, hormonal evaluation and response to different therapy lines were the studied. SPSS Statistics software was used for the analysis.

Results

A total of 89 patients were reviewed. The mean age at diagnosis was 51 ± 10.2 years, 57.3% were females. The mean maximal tumor diameter was 1.7 ± 0.65 cm, and up to 67.1% were macroadenoma. The MRI described cavernous sinus invasion in 19% of microadenoma and in 48% of macroadenoma. A total of 17 (19.8%) patients showed hyper-intense adenoma on T2- weighted MRI sequences, 13 (15.1%) are described as hypo-intense whereas 39(45.3%) appear to be isointense. Chiasmatic involvement was observed in 24 (28.9%). Basal insulin-like growth factor type 1 (IGF-1) above the upper limit of normal (ULN) and growth hormone (GH) levels after an oral glucose load (OGTT) (mean ± s.d.) were 678 ± 265 and 8.5 (1.5–20.7) ng/ml, respectively. Out of 89, 78 patients (80.9%) underwent surgery as primary treatment, the remaining cases required first-line medical treatment due to a rejection of surgical treatment or non-suitability because of high surgical risk. The histopathology report described proliferative marker Ki-67 $\leq$ 3% in 45 patients (Ki >3% in 10 patients). After surgical intervention, 74 patients continued in active followed up. Forty-seven of them (63.5%) were in disease remission (GH nadir on OGTT <0.4 ng/dl). Second line therapy was used for the 27 patients with persistent disease activity despite surgical resection. Five of them were treated with dopaminergic agonist another 16 with somatostatin receptors ligands (SRL), 2 with pegvisomant and the remaining 4 cases required a combination of SRL and cabergoline. A total of 24 patients (93%) showed IGF1 levels in normal range (5, 15, 2 and 2 for each therapy respectively).

Conclusion

Surgical intervention as the first line of treatment for patients with acromegaly achieves high cure rates. In those cases in which the disease is not cured, the available pharmacological treatments allow us to achieve disease control in practically all patients.

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EP724

Case report of a patient with partial antidiuretic hormone deficiency (central diabetes insipidus)

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Introduction

Diabetes insipidus (DI) is a rare condition characterized by excretion of large amounts of dilute urine and increased thirst due to deficiency or renal resistance of antidiuretic hormone (ADH). DI is often difficult to diagnose reliably and accurately, especially in patients with partial DI.

Aim

The aim of our case report is to present the patient with partial diabetes insipidus and to report the results of water deprivation and hypertonic saline stimulation tests.

Material and methods

18-year-old female patient was admitted to the hospital with chief complaints of increased thirst and urinary frequency after transnasal adenomectomy.

Results

In accordance with the results of water deprivation and hypertonic saline stimulation tests partial ADH-deficiency was diagnosed in our patient due to maximum urine osmolality of less than 539 mOsm/kg and 504 mOsm/kg, plasma osmolality 292 mOsm/kg and 311 mOsm/kg, maximum plasma sodium was 144,4 mmol/l and 143 mmol/l, respectively, and no change in urine osmolality after administration of 0.1 mg desmopressin sublingually.

Conclusion
Postoperative diabetes insipidus is often transient, which occurs as our data show in the gradual restoration of ADH secretion through the clinic of partial diabetes insipidus (ADH deficiency).

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EP725

Coexistence of PRL-secreting adenoma and germ cell tumor in 14-year-old adolescent

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Coexistence of different types of brain tumors is a very rare condition. We present a clinical case of PRL-secreting adenoma and germ cell tumor coexistence in 14-year-old adolescent. The patient was admitted to our Center with complaints of headache with nausea episodes, left-sided ptosis. Visual acuity was: visus OD = 1.0; visus OS = 0.6 Cyl -0.5 ax 70 = 1.0. Neuroimaging revealed supra-para(D,S)sellar mass 39 × 32 × 21 mm. Laboratory data revealed hypothyroidism, hypocortisolism and low prolactin level (43 mU/l). After 100-fold serum dilution (in order to exclude hook effect) prolactin level was 14 000 mU/l (*n* 60–510). Prolactinoma has been diagnosed and therapy with cabergoline (0.75 mg/week), hydrocortisone and levothyroxine was started. Two months after hospitalization visual acuity worsening has been noted and readmission was carried out. During second hospitalization, prolactin level became 4500 mU/l (after 100-fold serum dilution), MRI neuroimages showed a pronounced increase in the size of the neoplasm 78 × 52 × 48 mm. Levels of tumor markers were determined: hCG was < 2.39 mIU/ml (*n* 0–2.39), AFP was > 1000 IU/ml (*n* 0–5.5). Based on laboratory and instrumental data coexistence of PRL-secreting adenoma and AFP-secreting germ cell tumor was diagnosed. The patient was transferred to oncology department for immediate start of chemotherapy.

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EP726

Joint disease in patients with acromegaly

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Background
Acromegaly is a neuroendocrine disease that occurs with slowly progressive symptoms, which leads to delayed diagnosis and the development of complications. Arthropathy is one of such complications, which is accompanied by severe pain and significantly worsens the quality of life. The main attention of researchers is devoted to the pathology of the hip, knee and hand joints. At the same time, the study of the shoulder, acromioclavicular, costovertebral joints in acromegaly has not been carried out in detail.
Purpose
The objective of the study is to study damage of the shoulder, acromioclavicular, costovertebral joints in patients with acromegaly.
Materials and methods
The study included 31 patients (15 men and 16 women) with active acromegaly and 25 patients (12 men and 13 women) of the control group without acromegaly. Both groups had no trauma or rheumathoid disoders. The median age was 43.74 in patients with acromegaly and 46.64 in the control group. The duration of acromegaly at retrospective assessment ranged from 1 to 32 years, activity was confirmed by the results of the level of IGF-1 (median 577.98 ng/ml).
Results
In patients with acromegaly, arthrosis of the costovertebral joints was diagnosed 87% and did not depend on age and gender, in contrast to the control group, where the pathology of the costovertebral joints was detected in 64% of patients and there is a clear correlation with age. Arthrosis of the acromioclavicular joints was detected in patients with acromegaly in 32% of cases; these changes did not have a clear pattern with age characteristics and gender. In the control group, 16% over 55 years of age had pathology of the acromioclavicular joints, regardless of gender, and 8% of men under 55 years of age. In 54.8% of patients with acromegaly, arthrosis of the shoulder joints was found equally in women and men, and the defeat of these joints in the control group was registered only in 20% exclusively in males.
Conclusions
In patients with acromegaly, arthrosis of the acromioclavicular, costovertebral and shoulder joints is observed more often than in patients without this neuroendocrine pathology and does not depend on gender. The high frequency of joint damage in patients with acromegaly requires special attention to diagnosis, as it is an important component of quality of life.

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EP727

Prolactin-secreting pituitary adenoma: Clinical, radiological features and predictors of response to dopamine agonists

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Aim
Prolactinomas are the most frequent pituitary adenomas. Clear predictors of response to dopamine agonists (DA) are still discussed. The purpose of the study was to evaluate the clinical, radiological and hormonal characteristics of PRL-secreting pituitary adenomas, and to evaluate morphological changes over time and predictors of response to DA.
Patients and Methods
Patients affected by PRL-secreting adenoma undergoing DA therapy in follow-up in a tertiary care center (2000–2021) were retrospectively evaluated. Demographic (sex, age at diagnosis), clinical (BMI, cabergoline dose, surgery, symptoms at diagnosis), hormonal (PRL, pituitary function, hormone replacement therapy) and radiological parameters at diagnosis and during follow-up (major diameter, cranio-caudal, antero-posterior and latero-lateral diameters, adenoma volume, cavernous sinus invasion, optic chiasm compression, delta of adenoma diameter change) were collected. Subjects with ≥20% reduction in volume or major diameter were defined as responders. High-responders were those with ≥50% reduction.
Results
Sixty-two patients (median age 37 years, IQR 26.5–45.3) were included; most of the patients were female (62.9%), who had also more frequently microadenoma (82.6%, $P < 0.0001$). The median dose of cabergoline was 1.0 mg/week (0.5–1.4 mg/week). Forty-eight subjects (77.4%) were responders, 35 of whom (56.5%) were high responders. Response to therapy did not differ between sex or micro/macro lesions. Male patients and macroprolactinomas had higher early response rates (6–12 months) during follow-up ($P < 0.05$). An early (6-month) reduction in adenoma volume predicted a long-term shrinkage. Age, basal prolactin and cortisol levels were independent predictors of radiological outcomes.
Conclusions
Adenoma shrinkage and decrease in PRL levels can be useful predictors in the long-term workup management of prolactin-secreting lesions. They should be validated to drive early surgical intervention.

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EP728

Abstract withdrawn

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EP729

Features of pituitary macroadenomas with one size less than 10 mm

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There are clinical recommendations to conduct a hormonal investigation in all cases of pituitary tumors > 6 mm in size that seems to be uncertain.

The objective

To reveal features of pituitary macroadenomas with at least one size less than 10 mm

The materials and methods

We have analyzed medical records of 380 newly diagnosed patients with pituitary macroadenomas before any treatment: 162 non-functioning adenomas (NFAs), 74 prolactinomas, 144 somatotropinomas. Median patients' age was 56 [47; 63] y.o., 30 [25; 44] y.o. and 48.5 [35; 58] y.o., accordingly.

The results

The prevalence of macroadenomas with one size less than 10 mm were: 8/162 (4.9%) NFAs, 10/74 (13.5%) prolactinomas and 14/144 (9.7%) somatotropinomas. All patients were female except 2 men with somatotropinoma. The first complaints of patients with NFAs were headache – 6/8, in prolactinomas were menstrual disorders – 8/10 and in somatotropinomas were headache – 6/14, appearance changes – 4/14. The "first referred" specialists were: NFAs – neurologist (6/8); prolactinomas – gynecologist (8/10), somatotropinomas – therapist (10/14). Age at diagnosis was: NFAs 39.5 [27.8; 60.5] y.o., prolactinomas 25 [19.5; 27.5] y.o., somatotropinomas 52 [21; 67] y.o. ($P=0.009$). Compared to the general group of patients with relevant hormonal activity, patients with NFAs and prolactinomas were younger, and patients with somatotropinomas were older. Pituitary tumour volumes were: NFAs 470.3 [191; 807] mm^3, prolactinomas 384 [294; 564.4] mm^3, somatotropinomas 594 [355; 756] mm^3 ($P>0.05$). The pituitary macroadenomas were endosellar in 12/32 cases (4/8 NFAs, 5/10 prolactinomas and 3/14 somatotropinomas). Other different growth directions were suprasellar (3/8), laterosellar (3/10) and suprasellar (5/14), accordingly. Hypopituitarism (as secondary hypothyroidism) was diagnosed in 2/14 patients with somatotropinomas. Another 6 patients (4 – prolactinomas, 2 – somatotropinomas) had hypogonadism due to hyperprolactinemia.

The conclusions

Despite the small number of observations, we could describe some features of such pituitary "mini"-macroadenomas with one size less than 10 mm: mainly found in women; mainly found in prolactinomas and somatotropinomas; patients with NFAs and prolactinomas were younger and patients with somatotropinomas – older that general group of patients; in majority of cases had extrasellar extension. However, hypopituitarism was rare in such cases.

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EP730

Precision medicine in acromegaly: results of the ACROFAST study

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Medical treatment of acromegaly is currently performed through a trial-error manner using somatostatin receptor ligands (SRLs) as first-line drugs. Average SRLs response is seen in 50% of cases; subsequent drugs are indicated following clinical judgement. Some biomarkers either before or after surgical failure have been reported to predict SRLs response, including intensity in T2 weighted MRI, short acute octreotide test (sAOT), and different molecules such as SST2 and E-cadherin. We report the preliminary data of the ACROFAST study, a prospective trial based on the assignation of medical treatment according to SRLs response biomarkers compared to a control group.

Methods and subjects

Prospective clinical academic trial in which 21 university hospitals participated. Two protocols were compared in which the outcomes were time to control and percentage of subjects controlled at 6 and 12 months of treatment: A) a sequential protocol in which SRLs were started at mild doses (octreotide 20 mg and lanreotide 90 mg) for all patients and B) a personalized protocol in which SRLs were given as monotherapy (B1), in combination with pegvisomant (B2) or were replaced for pegvisomant as monotherapy (B3) according T2 MRI signal and sAOT in presurgical cases and the E-cadherin immunoexpression in tumor tissue in case of active disease after surgical treatment. B1 option included patients in which T2 MRI showed an hypointense signal, a GH at 2 h <2.7 ng/ml in the sAOT or had a full + immunostaining for E-cadherin. B3 option included cases in which MRI presented an hyperintense signal and sAOT GH decrease $<50\%$ over basal and in postsurgical failures, those – for E-cadherin; B2 were considered partial responders, in which sAOT showed a GH value at 2 h >2.7 ng/ml and $>$ 50% over basal together with an hypointense T2 MRI image, and in postsurgical intermediate positivity for E-cadherine.

Results

By December 2022, 73 patients have been recruited and 53 were evaluable, 27 in the personalized arm and 30 in the control sequential group. More patients in the personalized protocol 19/27 (70%) had achieved hormonal control compared to those in the sequential group – 14/30 (43%), $P<0.03$)- as well as in a shorter period of time: 263 days -8.8 months- vs 360 days -12 months- ($P<0.009$) for partial and resistant cases.

Conclusion

Personalized medicine is feasible by using a relatively simple protocol and allows a higher number of patients under control in less time since treatment initiation.

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EP731

Management of necrolytic migratory erythema with lanreotide a patient diagnosed with pancreatic glucagonoma: A rare case report

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Introduction

Glucagonomas are rare neuroendocrine tumours (NET). Glucagonoma syndrome is often misdiagnosed as other skin lesions by clinicians due to typical clinical sign of necrolytic migratory erythema (NME). In this article, we report a metastatic glucagonoma case diagnosed at adult age with distinct features of the disease.

Observations

We present a case of a 28-year-old female patient. The initial rash appeared in early 2019 and was mostly on lower extremities by the ankles, which were red

patches with irregular borders, intact and ruptured vesicles, and crust formation. The patient was prescribed several topical glucocorticoids and antimicrobials, but the rash was persistent and spread over her proximal lower extremities, back, chest, face and thus became generalized. By this 15 month interval the patient also developed symptoms of weight loss of 10 kg, nausea-vomiting, night sweats and abdominal-back pain. A skin biopsy was performed in 2020 and necrolytic migratory erythema was diagnosed. The patient then admitted to investigate glucagonoma. Admission laboratory measurements demonstrated no hyperglycemia but elevated blood glucagon levels (>700 ng/ml). Initial screening demonstrated a distal pancreatic lesion and overspread metastatic liver involvement. A liver biopsy was performed and the diagnosis of glucagonoma was established. The patient was initiated lanreotide 90 mg q28d and the dose was uptitrated to 120 mg q28d after 1 year. In this time interval generalized skin rash disappeared completely, and other symptoms improved. Then, she had recieved six doses of peptide receptor radionuclide therapy. Control imaging demonstrated that partial metabolic response. And, she underwent distal pancreatectomy and liver metastasectomy. Pathology report demonstated metastatic glucagonoma. Treatment of lanreotide 120 mg per/28 day was continued postoperatively. Imaging after 3 months showed multiple metastatic lesions over the liver. A chemotherapy regimen of capecitabine, temozolomide and bevacizumab was initiated. She is still receiving treatment and is in good performance condition.

Discussion

Clinicians should consider glucagonoma diagnosis based on the typical initial symptoms. An early diagnosis is critical for a better prognosis. Treatment options include somatostatin analogs, peptide receptor radioligand therapy, cytotoxic chemotherapy and surgery. In patients with unresectable metastatic cancers, a multidisciplinary approach is effective.

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EP732

Pituitary metastasis in neuroendocrine neoplasms, lesson learned from cases reports

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Introduction

Pituitary metastases (PM) are an uncommon manifestation of Neuroendocrine neoplasms (NENs) and are rarely reported. We report two cases of PM with different clinical lessons.

Case 1

A 37-year-old female underwent surgical resection for a high grade poorly differentiated neuroendocrine carcinoma of the cervix (Ki67 90%). Serial follow-up surveillance assessments revealed disease progression (local, liver, lung, and bone) for which she underwent different oncological therapies including chemo-, immuno- and radiotherapy. However, 4 years from initial diagnosis, she presented with frontal headaches and peripheral visual disturbance. MRI brain imaging revealed a 3 cm lesion within the pituitary Sella with suprasellar extension suggestive of pituitary metastasis. Treatment with dexamethasone led to symptomatic relief. Biochemistry was suggestive of secondary hypothyroidism (TSH 0.1 mU/l [0.55–4.78]; free T4 10 pmol/l [10–22]) and hypogonadotrophic hypogonadism (LH <1 mu/l; FSH 3 mU/l; oestradiol <70 pmol/l). Her pituitary lesion showed a marked reduction in size with the addition of carboplatin/paclitaxel (from 3 cm to 0.8 cm). Due to tumour size reduction and patient wishes, surgery was withheld. She was subsequently treated with external beam radiotherapy.

Case 2

A 64-year-old female diagnosed with a T2a N2 M0 lung NEN for which she underwent primary surgical resection (histology: well-differentiated grade 3 NEN [Ki67=25%]) with satisfactory postoperative cross-sectional and functional imaging. Within 12 months surveillance imaging showed bone metastases and she was commenced on lanreotide, Denosumab and external beam radiotherapy. Three months later she presented with headaches and visual disturbance; MRI brain showed 0.7 cm hypointense lesion on the pituitary gland. She was biochemically eupituitary and suspected to have an incidental pituitary adenoma. Surveillance imaging (4 months later) showed progressive increase in the size of the pituitary lesion (11 mm). Clinical symptoms and pituitary function tests revealed panhypopituitarism and DI (cortisol 84 nmol/l, ACTH <5 ng/l, TSH <0.02 mU/l, free T4 11.6 pmol/l, FSH 1 IU/l, LH 1 IU/l, serum osmolality 296 mOsm/kg [275–295], urine osmolality 87 mOsm/kg [>100], sodium 147 mmol/l [133–146], IGF-1 22 ng/ml [39–165]). She was treated with hydrocortisone, levothyroxine, and desmopressin. She underwent debulking surgery after multidisciplinary team discussion and post-operative histology was in keeping with a metastatic lung NEN. She is receiving postoperative radiotherapy.

Discussion

Pituitary metastases are rare but important in NENs and should be considered in patients with headaches, visual disturbances or features of hypopituitarism. The multimodal treatment for PM requires multidisciplinary input with individualized options being offered to the patient.

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EP733

Endogenous hyperinsulinemic hypoglycemia: A retrospective analysis of 10 cases

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Background and aim

Non-diabetic hypoglycemia is a rare entity that regroups several pathologies. Its exact diagnosis is mostly challenging. Endogenous hyperinsulinism is a curable cause that should be thoroughly screened. The objective of our study was to analyze the ethipathological aspects of hypoglycemia by endogenous hyperinsulinism.

Patients and methods

We conducted a retrospective study at the Endocrinology department of Hedi Chaker University Hospital, Sfax, Tunisia. We involved 10 patients investigated for endogenous hyperinsulinemic hypoglycemia, whose clinical, biochemical, and imaging peculiarities were collected from medical charts.

Results

Ten patients, 6 men and 4 women, with a mean age of 43 years (range 17–68 years) were included. The diagnosis of organic hypoglycemia was established based on Whipple's triad associating neuroglycopenic signs in all cases, a concomitant mean venous glycemia of 1.8 mmol/l (extremes: 1.2–2.8) with an improvement after glucose intake. Biological investigation results were consistent with an endogenous hyperinsulinemic hypoglycemia (a hypoglycemia concomitant to an insulinemia ≥3 mUI/l (average 19 mUI/l) and a C-peptide level ≥0.6 ng/ml (average 3 ng/ml). Topographic exploration had objectified a pancreatic lesion in 9 patients. All these patients underwent pancreatic surgery. The pancreatic lesion was histopathologically confirmed to be a well-differentiated neuroendocrine tumor in all cases. No pancreatic lesion was identified in one patient. This was a non-syndromic congenital hyperinsulinism most likely secondary to an ATP-sensitive potassium (KATP) channel defect.

Discussion

Non-diabetic hypoglycemia is a rare entity whose main etiology in adults is insulinoma. Congenital forms of hyperinsulinemic hypoglycemia can be transient or persistent, mild or severe. These conditions are present at birth and most become apparent in early infancy.

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EP734

The Strongest Clinical Tool is the Patient's Voice

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Introduction

As a Cushing syndrome (CS), patient myself and healthcare researcher I recognise that the patient's voice is the strongest weapon in a clinician's toolbox. Conducting a Doctor of Philosophy (PhD), study on a condition you have been diagnosed with was a journey of discoveries. My CS took almost 7 years to diagnose having been referred to a myriad of physicians prior to my definitive diagnosis. This was the driving force behind my desire to find out if other patients had similar experiences. This paper concentrates on a section of the disease-specific health-related quality of life (HRQoL), questionnaire specifically designed for my PhD study.

Method
Qualitative analysis was performed on open questions which were based on the members' perceived changes in their social and personal lives and any further information which they experienced, negative or positive as a consequence of their Cushing's illness. Thematic analysis of the textural content given in the answers was used to ascertain patterns (*themes*). Using the frequency results for the reasons given for a change, the emerging responses were coded in hieratical order to categorize the data. This process enabled the analysis of the common themes which emerged from the members responses. The frequency (%), of responses were displayed in Graphs and reported in themes. In addition, members were asked if they were satisfied with their clinician's ability to diagnose their CS.
Result
Eighty-six members of the Pituitary Foundation participated. *81%* found that their social lives had changed and *95.7%* their personal lives had also changed creating not only a physical but an emotional impact. The main reasons were their lack of sexual desire, body changes, anxiety, depression, mood swings, personality changes, exhaustion, fatigue, and suicidal ideation. Members felt that many physicians have little time to listen. This was reflected in *61.6%* who relied on their support groups and helplines to share their experiences and seek advice. Feelings of frustration, dismay were experienced by *43.3%*, expressing that their appointments were, "rushed," with very little information, advice and what to expect regarding the long-term effects. Families were often not invited to their consultations, and this led to a lack of understanding by their families.
Conclusion
Clinicians should apply listening skills as a master key in their toolbox leading to speedier diagnosis and treatment assisting them to not only focus on the disease but adopt a patient-centred approach to treat patients as an individual with unmet needs.

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EP735

Predictive clinical factors of stature gain in congenital growth hormone deficiency treated patients

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Background and aim
The management of Congenital Growth hormone deficiency (CGHD) is based on hormonal substitution with recombinant GH. The stature prognosis may be affected by several clinical, genetic, and therapeutic factors. This study aims to assess the predictive clinical factors of stature gain in CGHD-treated patients.
Patients and Methods
We conducted a retrospective study (1991–2019) at the Endocrinology department of Hedi Chaker University Hospital, Sfax, Tunisia. We involved 87 patients diagnosed with CGHD, whose clinical, biochemical, and imaging peculiarities were collected from medical charts.
Results
The mean age at diagnosis was 14 years, with a male predominance (59%). The most frequent reason for consultation was short stature (75%). The median height was 131 cm. The bone age was behind the chronological age in all cases. The average bone age delay was 48 months. GH substitution was indicated in 60% of cases. The stature gain was significantly associated with the severity of the growth retardation, combined hypopituitarism, pituitary hypoplasia, and pituitary stalk abnormalities as shown in Table 1. The female gender was strongly predictive of reaching the target adult height (Table 2).
Discussion
To optimize stature prognosis in CGHD patients, all studies have tried to find factors that predict good responders to GH treatment. Multivariate analysis in the KIGS study established a strong correlation between parental target height and growth rate in the first year of treatment and stature gain. According to the French registry, younger age at the initiation of treatment, delayed bone age, and severity of DGH were positive predictive factors for stature gain, which is in line with our results.

Table 1: Predictive clinical factors of stature gain in CGHD-treated patients

Studied factors		Mean stature gain (s.d.)	*P*-value
CGHD	**Isolated**	1.1±1	**0.009**
	Combined	1.8±1.4	
CGHD	**Total**	1.4±1.3	0.773
	Partial	1.3±0.9	
Abnormal MRI imaging		1.8±1.4	**0.028**
Pituitary Hypoplasia		1.9±1.4	**0.015**
Pituitary stalk interruption		2.1±1.2	**0.019**
Ectopic posterior pituitary		1.5±1.4	0.792

Table 2: Factors predicting the achievement of target height in CGHD-treated patients

Studied Factors		Target Height		*P*-value
	Achieved	**Non achieved**		
Gender	**M**	*N*=3/9	*N*=29/39	**0.044**
	F	*N*=6/9	*N*=10/39	
Age at diagnosis (years)		12.3±2.2	10±3.8	0.105
Age at treatment initiation (years)		13±2.8	11.3±3.4	0.184
Height at treatment initiation (cm)		132.7±9.4	124±17	0.203
Treatment duration (months)		30±12.3	48.4±29	0.114

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EP736

Morphological pituitary abnormalities in patients with congenital Growth Hormone deficiency

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Background and aim
Disorders of the development of the pituitary gland could result in some forms of Congenital Growth hormone deficiency (CGHD). This study aims to assess the morphological abnormalities of the pituitary gland in patients with CGHD.
Patients and Methods
We conducted a retrospective study (1991–2019) at the Endocrinology department of Hedi Chaker University Hospital, Sfax, Tunisia. We involved 87 patients diagnosed with CGHD, whose clinical, biochemical, and imaging peculiarities were collected from medical charts.
Results
The mean age was 14 years, with a male predominance (59%). Seventy-five percent of patients were referred for short stature. We noted a delayed diagnosis in 65% of cases. The median height was 131 cm. Severe growth delay was noticed in 38.6% of cases. The average delay of bone age was 48 months. Eighty percent of CGHD patients combined hypopituitarism. A positive correlation was established between the precocious onset of the pituitary dysfunction and the presence of pituitary hypoplasia ($P=0.009$), as well as with the severity of growth retardation ($P=0.016$) and the number of affected axes ($P=0.02$). The latter correlation was significant when three or more pituitary axes were involved, which also remained significant for pituitary stalk anomalies. Posterior pituitary ectopy was inversely correlated with the age of discovery of hypopituitarism ($P=0.001$) but not with neonatal distress ($P=0.28$).
Discussion
The hypoplastic pituitary is the most common morphological abnormality in patients with CGHD since GH-secreting cells represent the largest cell population in the pituitary gland. In our cohort, 49.4% of CGHD cases had pituitary hypoplasia. Similar findings were reported in literature where hypoplasia was noted in 59% to 61% of patients. Pituitary stalk abnormalities expose the affected patient to a 3.28-fold increased risk of progression to combined forms of hypopituitarism.

Table 1: Predictive clinical factors of pituitary abnormalities in patients with CGHD

Studied factors	Normal pituitary	Pituitary Hypoplasia	*P*-value
Age at diagnosis (years)	14	11	**0.009**
Severe statural retardation	61%	84%	**0.016**
Number of hypopituitarisms	2.3	3.1	**0.02**
Severity of GHD	46%	54%	0.16

Table 2: Morphological pituitary abnormalities and the number of hormonal dysfunctions in patients with CGHD

Hormonal dysfunctions	Normal pituitary	Pituitary hypoplasia	Pituitary stalk abnormality
Isolated CGHD	64%	35%	11%
2 axes	68%	31%	18%
3 axes	50%	50%	27%
4 axes	33%	66%	60%
5 axes	11%	88%	66%
***P*-value**	**0.037**	**0.037**	**0.001**

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EP737

Predicting the risk of developing cerebrospinal fluid fistula in patients with prolactinoma

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Introduction
Prolactin secreting pituitary adenoma represents the most common functioning pituitary neoplasm with a clinical picture that includes amenorrhea, galactorrhea and infertility. Tumor size may vary from microadenomas amendable to medical therapy with dopamine agonists to macroadenomas with difficult management. Complications are usually related to tumor size and most frequently include hypogonadism alone or associated with other pituitary deficiencies, visual field defects, headache and cranial neuropathies. Cerebrospinal fluid fistula represents a rare but severe finding that can complicate the evolution of prolactinomas.
Materials and methods
We report three cases of prolactinomas complicated with cerebrospinal fluid leak either spontaneously or during the course of treatment. The patients were all males, with age between 22 and 66 years and high tumor volume and prolactin values at diagnosis. The first patient presented with bitemporal hemianopia with an 86/77/64 mm sellar mass invasive into the suprasellar region and both sphenoid sinuses and a prolactin value at diagnosis of 11 432 ng/ml. He developed cerebrospinal fluid fistula after 9 months of treatment with cabergoline, at the attempt of increasing the dose from 3 mg/week to 4.5 mg/week. The second patient was diagnosed with pituitary macroadenoma on cerebral CT starting from clinical features that included headache, visual field defects and hypogonadism and performed transfrontal adenomectomy as first line therapy. His postoperative course was complicated by transient diabetes insipidus, hypopituitarism and cerebrospinal fluid leak that required surgical repair. Diagnosis of prolactinoma was established at the postoperative evaluation due to high levels of prolactin of 10 635 ng/ml and received treatment with dopamine agonists. The third patient presented with spontaneous rhinoliquorrhea and an invasive pituitary tumor of 67/45/44 mm. He performed transsphenoidal debulking of pituitary adenoma and surgical repair of the sellar floor. Postoperative, diagnosis of prolactinoma was made, with a prolactin value of 18 638 ng/ml and treatment with cabergoline was initiated.
Discussion
Cerebrospinal fluid fistula is a life-threatening condition associated with a high risk of developing meningitis, intracranial abscess and pneumocephalus. Postulated mechanisms are invasive pituitary macroadenomas with bone destruction in the sellar floor. Tumor shrinkage induced by medical or surgical treatment uncovers the bone defects leading to cerebrospinal fluid rhinoliquorrhea. Surgical repair via a transphenoidal approach is mandatory and long term follow-up is usually needed.

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EP738

Pituitary macroadenoma, incidental finding after soccer match

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Introduction
Thyrotropin-secreting pituitary tumors (TSH-omas) are a rare disorder and an infrequent cause of hyperthyroidism. The prevalence in the general population being 1 to 2 cases per million. However, recents studies have demonstrated an increase of TSH-omas over time. The increased number of cases principally results from the ultrasensitive TSH immunometric assays and from improved general practioner endocrinologist awaress. There is an inappropriate secretion of TSH due to autonomous and refractory to the negative feedback of thyroid hormones. In about 30% of patients with pituitary adenomas, hypersecretion of other pituitary hormones can be detected. The most frequent associations are the hypersecretion of GH and/or PRL.
Clinical case
A 28-year-old woman attended the emergency room by left hemicranial headache after accidental head injury in a soccer match. Pituitary MRI found a pituitary macroadenoma (18.5×25×31.5 mm). There are no symptoms of amenorrhea or galactorrhea. She also didn't complain of symptoms of tachycardia, tremor or weight loss. She didn't refer changes in shoe or ring size. On examination, there is no goiter or other stigmata of endocrine dysfunction. Laboratory evaluations showed central hyperthyroidism (FT3 6.85 pg/ml, FT4 1.98 ng/dl, TSH 6.66 mU/l), circulating free alpha-GSU elevation (> 9 mUi/l), insulin-like growth factor elevation (IGF-1 237 ng/ml) and hyperprolactinemia (PRL pool 64.97 ng/ml). TRH stimulation test was performed and TSH and alpha-GSU levels didn't increase after TRH injection. GH nadir concentrations after 75 mg oral glucose tolerance test (OGTT) was ≥1 µg/l. Therefore, hypersecretion of thyrotropin and GH was confirmed. Hyperprolactinemia was attributed to pituitary stalk compression. The patient was prescribed the somatostatin analogues (somatuline autogel 60 mg every 28 days). After 1 month of treatment, IFGF-1 level decreased to 180 ng/ml and normalitation thyroid function (FT3 2.48 pg/ml, FT4 0.97 ng/dl, TSH 2.48 mU/l). Somatuline autogel dose was titrated up to 120 mg every 60 days. After 3 months of treatment, tumor size has been reduced (18×19×16 mm). A transnasal adenoidectomy was performed with restoration of euthyroidism and normalization of IGF1 and PRL levels. Preserved pituitary function after surgery resection. The pathological anatomy showed positive cells for synaptophysin, CAM 5.2 TSH and GH.
Conclusions
TSH-omas are rare pituitary tumors but the use of ultrasensitive immunoassay methods and the increase in imaging tests allow early diagnosis. Treatment with somatostatin analogues may be useful to reduce hyperthyroid signs and symptoms, as well as the adenoma size.

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EP739

Homocysteine levels in acromegaly patients: comparison of active disease with remission

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Objective
Acromegaly is associated with increased cardiovascular mortality. Hyperhomocysteinemia has been associated with cardiovascular disease, lower-extremity peripheral arterial disease and heart failure. Data on the prevalence of hyperhomocysteinemia and peripheral arterial disease in patients with acromegaly is still limited. The aim of this study was to compare serum homocysteine levels between acromegaly patients with active disease and remission, and to evaluate presence of peripheral arterial disease.
Material and Method
A single-center, cross-sectional study was conducted in patients with acromegaly. Patients were compared with respect to their serum homocysteine levels, clinical and metabolic parameters, and ankle brachial index (ABI). Patients who had folate, vitamin B6, or vitamin B12 deficiency; chronic kidney disease; using drugs that change homocysteine levels were not included in the study.
Results
A total of 31 patients (19 female/12 male), diagnosed with acromegaly were recruited for this study. Patients were divided into two groups: active disease (group 1, $n=18$) and remission (group 2, $n=13$). Fasting blood glucose level were higher in group 1 than group 2 (111 ± 22.3 vs. $93\pm10,9$ mg/dl, respectively, $P=0.01$). Only one patient had low ABI whose homocysteine level was normal. ABI were similar between the active disease and remission groups. Homocysteine levels were high in 12 (37.5%) patients (6 in group 1 and 6 in group 2) and body mass index was higher in pateints with elevated homocysteine levels (29.6 ± 3.8 vs. 26.8 ± 3.7, $P=0.04$). Although ABI were not correlated with homocystein levels, especially systolic blood pressure in both posterior tibial arteries were low ($P=0,048$).
Conclusion
This study revealed that high homocysteine levels are associated with increased body mass index. Since acromegaly patients more prone to risk of cardiovascular disease, it is important to examine all possible risk factors in these patients.

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EP740

Pituicytoma – case report of an extremely rare and little-studied primary tumour of the adult neurohypophysis

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The pituicytomas are extremely rare and little-studied primary tumours of the adult neurohypophysis. These are low-grade (World Health Organization [WHO] grade 1), indolent gliomas which present as a sellar mass, which is usually mistaken for a pituitary adenoma, and has no known hormonal secretory function. A 63 years old retired paediatrician was referred to the neurology clinic with the

history of constant severe headache ongoing for a few weeks. It involved the whole of the head and was associated with dizziness. There were no postural symptoms and no history of vomiting or nausea or any signs of raised ICP. His past medical history included hypertension, cataract and glaucoma. An urgent MRI head, requested by Neurology, revealed a pituitary lesion which was not fully characterised. He subsequently had a pituitary MRI which showed left sided pituitary adenoma of 7×8×8 mm size with areas of previous haemorrhage. He was urgently seen in Endocrinology clinic and the blood test for anterior pituitary profile were normal. MRIs at the intervals of 6 months and then 18 months showed a slow growth in the tumour size to 15×11 mm with the compression on the right optic chiasm. Formal visual field test showed normal field of vision in the right eye and a stable defect in the left eye. This case was discussed in pituitary MDT and it was thought to be likely craniopharyngioma at that point. Transsphenoidal surgery was offered due to enlarging lesion and constant headache. Surgery was aimed at significant debulking and it went well without any complications. Histology report confirmed pituicytoma. Patient remained very well and his symptoms of headache resolved with an improvement in his vision and visual field. His pituitary function remained normal. Patient was interested to explore the options of radiosurgery or radiotherapy for the remnant part of the cytoma. His case was discussed in the pituitary MDT at another centre which admitted that there was paucity in experience with a rare tumour like pituicytoma and advised to continue conservative approach and to consider repeat surgery or SRS if the growth recurs. It has been a very interesting case for Endocrinology, Neurosurgery, Radiology and Oncology teams who have been involved in his care. Patient, being a doctor himself, had a very good understanding of his condition and was aware of the rare nature of the tumour. We continue to follow him up in our Endocrine clinic.

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EP741

Vitamin D status and cardiovascular risk in a cohort of acromegalic patients

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Background
Vitamin D deficiency is the most common nutritional deficiency, estimated to affect almost one billion people worldwide. Multiple factors influence 25(OH)D levels: nutrition, sunlight exposure, outdoor physical activity, skin color. Patients with active acromegaly (AA) have lower 25(OH)D levels compared with healthy population and are at a higher risk to develop vitamin D deficiency. Also, some studies have suggested a possible protective role of vitamin D on the cardiovascular system.
Aim
To assess the impact of vitamin D deficiency on cardiovascular disease risk (CVD) in patients with acromegaly from Romania, a country situated in northern hemisphere at latitudes greater than 40°N.
Methods
Retrospective study by analyzing the files of patients with confirmed acromegaly who underwent treatment in a tertiary endocrine center. 134 patients (91F/43M) were included. IGF1, GH, 25(OH)VitaminD were measured by chemiluminescence either at diagnosis of acromegaly or throughout the follow-up. Total, LDL ad HDL cholesterol, triglycerides, serum glucose, HbA1c, blood pressure were also measured and the acromegaly activity was assessed according to the newest guidelines. The ACM patients were divided into three subgroups: active acromegaly (AA), controlled acromegaly (CA) and cured acromegaly. The cardiovascular disease (CVD) risk has been assessed at the moment of vitamin D dosage using European's Society of Cardiology (ESC) CVD risk tool.
Results
Globally, 95 patients had AA, 30 patients-CA, 3 patients were cured, whilst for 6 patients there was not enough information to quantify their acromegaly status. Mean age at vitamin D dosage was 51.3±12.4 years. AA patients had more frequently normal total cholesterol and triglycerides values if their 25(OH)D was over 20 ng/ml ($P=0.008$ respectively $P=0.05$; chi-sq). AA women also had more frequently normal cholesterol values if their 25(OH)D levels were > 20 ng/ml ($P=0.01$; chi-sq). No differences were found between vitamin D and lipid profile in the other 2 subgroups, regardless of gender. However, after excluding diabetic acromegalic patients, when calculating the personal risk profile for each AA patient ($N=53$, F+M) using ESC CVD Risk tool and classifying them into low, moderate and severe risk according to age, subjects with 25(OH)D < 20 ng/ml levels had more frequent a moderate and severe 10-year CVD episode risk ($P=0.03$; chi-sq).
Conclusion
Patients with active acromegaly may benefit from dosing the 25(OH)D levels and, if needed, prescribing supplementation may help. Therefore, further prospective studies evaluating the impact of vitamin D levels on CVD risk are necessary to confirm these findings definitively.

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EP742

Hyponatremia apparently due to carbamazepine as the initial presentation of panhypopituitarism in a patient with a non-functioning pituitary tumour

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Introduction
Hyponatremia, defined as a serum sodium concentration below 135 mEq/l, has a heterogeneous etiology, the main endocrine causes includind the syndrome of inappropiate antidiuresis (SIAD), adrenal insufficiency and severe hypothyroidism.
Materials and methods
Clinical, hormonal and imaging evaluation
Aim
To present a case of hyponatremia leading to the diagnosis of a large pituitary tumor
Case presentation
A 61 year-old male with a history of grandmal epilepsy treated with carbamazepine 600 mg/day, arterial hypertension, type 2 diabetes mellitus on oral antidiabetic drugs, obesity and dyslipidemia, presented initially to the ER for fatigue, nausea and emesis. Three weeks prior to presentation, he had undergone a laparoscopic intervention for an inguinal hernia. Physical examination revealed hypotension (BP=90/70 mmHg). Serum biochemistry revealed severe hyponatremia (107 mEq/l), hypochloremia and hypokalemia (2.5 mEq/l). Causes of pseudohyponatremia (hyperglycemia, hyperlipemia and hyperproteinemia) were ruled out. A cerebral CT scan demonstrated a pituitary tumor (2.1/2.7/3.1 cm) invading the right cavernous sinus. Biochemical tests of pituitary function demonstrated hypogonadotrophic hypogonadism and possible hypocortisolemia (5.8 µg/dl at 1300 h). Immediate administration of 3% NaCl and replacement of carbamazepine (a known SIAD cause) with levetiracetam led to gradual improvement. Ten days after initial presentation, the patient was admitted to our department for complete endocrine workup. On admission, clinical status was unremarkable, except for a right eye temporal visual field defect. Laboratory tests demonstrated panhypopituitarism and normoprolactinemia. His general status improved upon glucocorticoid replacement therapy followed by thyroid replacement. Ophtalmological examination showed optic chiasm syndrome, with right eye temporal hemianopia and left eye temporal and inferior quadrantanopia. The pituitary MDT recommended a pituitary MRI and neurosurgical evaluation, which are pending.
Conclusions
Our case illustrates the incidental discovery of a pituitary tumour and hypopituitarism in a pacient who already had a plausible cause of SIAD. Awareness of various causes of hyponatremia and attention to clinical detail are critical for detecting the complete etiology, which determines appropriate treatment in hyponatremia.

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EP743

Survey on caregivers' experiences and perspectives on children's daily growth hormone treatment

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Background and objective
Human recombinant growth hormone (hrGH/GH) is an injectable medication used commonly for growth hormone deficiency (GHD) and other health conditions that reduce growth and adult height. Daily GH injections can burden families and result in poor adherence. This study was conducted to investigate caregivers' experiences, attitudes and preferences regarding pediatric GH treatment. At the time of data collection, the long-acting GH products were not available on the market.
Methods
This survey to the caregivers of under-aged patients using GH was conducted in 50 community pharmacies across Finland between June 2021 and April 2022. Caregivers were identified in pharmacies when purchasing GH. They were asked to complete an anonymous semi-structured electronic questionnaire on a tablet computer.
Results
Total of 78 caregivers responded to the survey. Mean age of the children on GH treatment was 10.1 years (range 2–17 years). Two thirds (65.4%) of them were boys. Most common indications for GH treatment were GHD (67.9%) and small for gestational age without catch-up growth (10.3%). Two thirds (67.9%) of children had been using GH for 3 years or longer, and one third (32.1%) for 2 years or less. All caregivers were very satisfied (70.5%) or quite satisfied (29.5%) with the GH treatment. However, three out of four caregivers (74.4%) reported at least one challenge related to the GH treatment. The most common challenges were administration by injection (35.9%), cold storage requirement (35.9%), high price (16.7%) and child's unwillingness to take GH (10.3%). Caregivers were asked to describe in their own words an as good and well functioning GH treatment they can think of. Open answers were categorized and quantified. Most frequently mentioned attributes were less frequent dosing interval (25.6%), storage in room temperature (24.4%) and easy-to use dosing device (23.1%). Also good response (11.5%), different administration route, such as cream or tablet (9.0%) and few adverse effects (7.7%) were mentioned.
Conclusions
All caregivers were satisfied with the GH treatment. However, nearly 75% of the responders identified treatment-related challenges. The most frequently reported challenge was the mode of administration (injection). When describing optimal GH treatment, the wish for a less frequent dosing interval was the most often mentioned. Data from this survey can provide support in selecting the optimal type of GH treatment for paediatric and adolescent patients.

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EP744

Growth hormone treatment tends to promote hepatic VLDL1-triglyceride export in humans

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Introduction
Non-alcoholic fatty liver disease (NAFLD) is a systemic, metabolic condition associated with increased morbidity and mortality. Defined by an increase in hepatic lipid content (HCL), NAFLD develops in consequence of lipid oversupply and/or a diminished disposal of hepatic lipids. The latter may include an impaired export of triglycerides (TG) via the secretion of very-low density lipoprotein1 (VLDL1) particles, an important mechanism of the liver to protect itself from steatosis. Growth hormone (GH) is known for its beneficial effects on body composition and increases lean body mass by favouring overall lipid consumption. Furthermore, studies in acromegalic patients suggest excessive GH secretion to decrease HCL. Although current data are conflicting, GH might mediate the reduction of HCL by fostering the export of TG rich VLDL1 particles.
Aim and methods
We aimed to determine the impact of exogenous GH treatment on hepatic TG export, hypothesizing an increase of VLDL1-TG secretion after short-term GH excess. Therefore, using an intralipid infusion protocol, VLDL1-TG secretion was assessed in five healthy, male volunteers (age 26.8±4.7 years; BMI 23.8±3.8 kg/m^2) at baseline and after one week of GH treatment with daily injections of 2 mg Genotropin®. Parameters are given as mean ±standard deviation and paired *t*-test was used for analysis.
Results
After one week of GH treatment, secretion of VLDL1-TG increased in four of five cases, depicted by a mean increase of 10.5% (687.8±289.2 vs. 813.2±518.8 mg/h, $P=0.294$). Marked increases in serum IGF-1 (231.2±22.3 vs. 480.4±101.8 ng/ml, $P=0.009$), insulin (8.3±3.1 vs. 16±3.6 µIU/ml, $P=0.021$), and C-peptide (1.8±0.3 vs. 2.5±0.7 ng/ml, $P=0.088$) indicated a sufficient impact of GH dosage.
Future perspective
This preliminary analysis shows a trend towards increased VLDL1-TG secretion in response to short-term subcutaneous GH treatment in humans. Further investigation of GH-mediated hepatic TG export might pave the way for novel therapeutic strategies in the treatment of NAFLD.

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EP745

Patient-centric design of the lonapegsomatropin auto-injector for pediatric growth hormone deficiency

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Background
Lonapegsomatropin (SKYTROFA™; TransCon hGH), an FDA and EMA approved once-weekly prodrug of somatropin for pediatric growth hormone deficiency (pGHD), uses TransCon® technology to transiently link an inert carrier to a parent drug to achieve sustained release. Daily growth hormone injection, standard treatment for pGHD for decades, may be associated with challenges including needle anxiety and low adherence. The lonapegsomatropin Auto-Injector, winner of two innovation awards for drug delivery and patient-centric design, was developed through user testing and feedback to complement weekly lonapegsomatropin and minimize challenges in reconstitution and injection. Key design features of the Auto-Injector include a hidden needle, empty-all cartridge design, and icons to indicate and guide completion of all steps.
Aim
The lonapegsomatropin Auto-Injector was evaluated under simulated use conditions as outlined in FDA guidance: "human factors and usability engineering processes are performed to maximize the likelihood that new medical devices will be safe and effective for the intended users, uses and use environments… without serious use errors or problems."
Methods
Usability of the lonapegsomatropin Auto-Injector was evaluated in trained and untrained patients (pGHD or other chronic conditions requiring injection,) caregivers, and health care providers (HCPs) responsible for giving injections or training patients/caregivers. Auto-Injector, cartridges, packaging, instructions for use (IFU), quick reference guide, helpline, and training video were available for self-exploration. Participants were evaluated on device use, charging, and comprehension of IFU.
Results
All participants, (120 children and caregivers, 60 injection-naïve, and 15 HCPs) were able to complete an injection successfully with the lonapegsomatropin Auto-Injector. Usability issues observed for injection tasks for all participants were low and comparable to typical observations in usability studies: patients (3.2%), caregivers (2.4%), and HCPs (2.8%). All participants reported they could follow the instructions as written and 98% of participants felt they could use the device as intended on their own or with supervision (patients only).
Conclusions
The patient-centric design of the award-winning lonapegsomatropin Auto-injector leads to successful, confident usage in which participants can follow the instructions to deliver an injection as intended. Together with once-weekly lonapegsomatropin, the lonapegsomatropin Auto-Injector may overcome challenges in treatment of pGHD such as needle anxiety and difficulties with

injection, with the potential to improve adherence which has been shown to impact outcomes in real-world use.

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EP746

Tumor mimicking ampullary carcinoma in a patient with acromegaly

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Introduction
Acromegaly is the set of clinical manifestations induced by chronic exposure to an endogenous excess of growth hormone (GH). Most often, acromegaly is related to GH production by a pituitary adenoma. It may be associated with neuroendocrine tumors of the pancreas as part of multiple endocrine neoplasia type 1 (MEN1). Herein, we described a tumor mimicking a carcinoma of the Ampulla of Vater in a patient with acromegaly.
Observation
A 54-year-old patient has an over 13-year history of acromegaly secondary to a pituitary macroadenoma of 21 mm with lateral extension to the left cavernous sinus. His acromegaly was complicated by diabetes mellitus, hypertension, colonic diverticulosis, and an EU-TIRADS III thyroid nodule. The patient underwent a transsphenoidal surgery that was complicated by transient central diabetes insipidus and a corticotropin deficiency. IGF-1 levels remained elevated postoperatively although the absence of residual tumor. Hence, monthly octreotide injections were prescribed complicated by a vesicular lithiasis operated 5 years ago. During follow up, the patient presented one year ago epigastralgia associated with jaundice, elevated liver enzymes and cholestasis. An abdominal MRI revealed ampullary carcinoma that was ruled out later histologically after pancreaticoduodenectomy.
Discussion
Acromegaly is a chronic, progressive and systemic disease that requires long-term treatment and follow up. Its association with a carcinoma of the Ampulla of Vater, which is a tumor with a poor prognosis, was not reported in the literature, contrary to the neuroendocrine tumors of the pancreas. A biopsy of the inflammatory tumor in our patient would prevent a major surgery.

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EP747

Immune landscape of peripheral blood mononuclear cells in patients with Cushing's syndrome and mild autonomous cortisol secretion

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Background
Endogenous Cushing's syndrome (CS) is associated with increased susceptibility to infections and mortality. Previously reported effects of hypercortisolism on immune function include a reduced CD4+/CD8+ ratio with a shift towards IL4+T helper cells (Th2), suppressed NK-cell cytotoxic activity as well as a low-grade inflammatory profile.
Aim
This cross-sectional single center study aims to compare immune phenotype in patients with overt CS, mild autonomous cortisol secretion (MACS), CS on long-term adrenostatic treatment (> 5 months, LAT) and healthy controls.
Methods
T- and NK-cell subsets from peripheral blood mononuclear cells (PBMCs) isolated by density gradient centrifugation were analyzed using multicolor flow cytometry in 20 overt CS, 15 MACS, 15 LAT patients and 63 age and sex matched healthy controls.
Results
We found a significant reduction of CD4+/CD8+ ratio in patients with overt CS (median 1.7, IQR 0.65) and LAT (median 1.61, IQR 0.89), compared to healthy controls (median 3.18, IQR 2.43), with a significant shift towards Th2 differentiation. In contrast, there was no significant reduction of CD4+/CD8+ ratio in MACS (median 2.47, IQR 1.4), while the shift towards Th2 differentiation was still significantly present. FoxP3+ regulatory T cells (Tregs) and the overall NK-cell count were significantly reduced in patients with overt CS, LAT and MACS ($P<0.0001$), compared to healthy controls, with upregulated CD56dimCD16bright NK-cells and CD107a expression. Patients with overt CS presented with a significant reduction of activating ($P=0.0028$) and inhibitory ($P=0.0161$) NK-cell receptors. Patients on LAT and patients with MACS were found to have reduced NKp46 expression ($P<0.0001$) with no significant change in inhibitory NK-cell receptors, overall outweighing the presence of activating NK-cell receptors.
Conclusion
Altered CD4+/CD8+ ratios in patients with overt CS and LAT suggest a higher susceptibility to opportunistic and viral infections. The suppression of Tregs implies a chronic inflammatory state in all patient subgroups. Upregulation of cytotoxic NK-cell subsets may be a compensatory mechanism to suppression of activating NK-cell receptors. Changes in immunophenotype found in patients with MACS indicate less pronounced alterations compared to overt CS. Immunophenotype of patients with CS appears to be unchanged by LAT.

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EP748

Clival prolactinoma: A case report

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Introduction
Ectopic pituitary adenomas (EPAs) are extremely rare intracranial tumors. Since 1909, few cases has been reported in the literature. We report a case of clivus prolactinoma.
Case report
A 52-year-old women with a history of infertility, presented one year ago at the emergency with headaches and a sudden decreased visual acuity. The pituitary MRI revealed an arachnoidocele, pituitary adenoma of the left cavernous lodge measuring 20×18×17 mm, with ectopic development in the clivus. Pituitary workup showed a hyperprolactinemia at 225 ng/ml, a cortisol level 60 min after synacthen at 517.3 nmol/l, but a peripheral hypothyroidism with a high TSH level at 9.6 µUI/ml and a low FT4 level at 12.2 pmol/l normal range (12–22). The evolution was marked by a spontaneous resolution of hedaches and total visual recovery. Thus, a medical treatement was decided.The patient has recieved dopamin agonists with prolactin normalisation but persistance of the same tumor's size.
Conclusion
Clival tumors represent 1% of intracranial neoplasms. EPAs are thought to originate from remnants of the embryological migratory path of the pituitary gland.In the literature review, the most diagnostic presentation of clival adenomas are headache. Focal neurological deficits can be seen in case of the compression of adjacent structures. Clival adenomas are functional in 75% of cases, prolactin-secretion is the most frequent. Pharmacotherapy is the first line treatment but the results are discordants.

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EP749

A case of Turner syndrome associated with growth hormone deficiency

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Background
Turner syndrome (TS) is an important cause of short stature, however, there are a few reported cases of concomitant occurrence of TS and growth hormone deficiency (GHD).
Case report
We report a 23-year-old female with concominat TS and GHD, also presenting partial FSH/LH deficiency and primary myxedema. The patient had iniatially been evaluated at the age of 15 for short stature and primary amenorrhea when she was diagnosed with Turner syndrome (45 X karyotype) and primary hypothyroidism, but didn't comply with treatment and follow-up recommendations. At clinical examination she was 130 cm (−5.4 SDS) and 47 kg in weight with proportionate dwarfism, dysmorphic facial features, webbed neck, brachydactyly, broad chest with wide-spaced nipples, genu valgum, flat feet, secondary sexual characters rated B2, P1 according to Tanner's classification. Bone age was 9.5 years. Biochemical tests revealed: FSH = 22.36 UI/l (n = 3.85–8.78), LH = 1.69 UI/l (n = 2.12–10.89), Estradiol = 18.36 pg/ml (n = 22.4–115); IGF-1 = 88.42 ng/ml (n = 103–326); PRL = 28.7 ng/ml (n = 3–26.72); freeT4 < 5.15 pmol/l (n = 9–19), TSH > 100 uUI/ml, ATPO > 1000 UI/ml. Other hormone levels were within normal ranges. The serum ionogram, glucose, hepatic and renal function were also normal. Abdominal CT scan excluded renal anomalies. Echocardiogram was normal. The patient received Levothyroxine 75 µg/day with progressive normalization of thyroid hormone profile. During the next 3 months, PRL level normalized, but FSH (22.45 U/l) and LH (7.19 U/l) values indicated persistence of partial gonadotropin deficiency. Considering the severe short stature, we evaluated GH response in ITT, with peak GH after insulin induced hypoglycemia of 0.31 ng/ml demonstrating GH deficiency. Sella MRI showed adenohypophysis of normal size, convex cranially and inhomogeneous basally on the left side by the presence of a microadenoma of 6.5/4/7 mm. We considered the bone age of 9.5 years and unfused epiphyseal plates demonstrating growth potential and the rhGH therapy was initiated, at a dose of 30 µg/kg per day given by subcutaneous injection. The initiation of estrogen replacement therapy was postponed in function of the patient's growth velocity. In a 3 month follow-up she grew 1.8 cm in height.
Conclusions
We presented a patient with Turner syndrome with severe short stature by concomitant GH deficiency; in this case with a non-functioning pituitary microadenoma, we can not exclude the hyperplasia of the TSH-producing cells associated with a long time untreated primary myxedema as a supplementary cause of GH deficiency. We will perform the long-term follow-up with close monitoring of rhGH therapy.

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EP750

Sheehan syndrome revealed by acute adrenal insufficiency 3 months after the delivery

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Introduction
Sheehan syndrome (SS) is a hemorrhagic necrosis of the pituitary gland responsible of anterior pituitary insufficiency. It occurs in a context of cerebral hypo flow due to a rapid blood pressure drop and/or acute hemorrhagia. We report a case of SS revealed by acute corticotropic insufficiency.
Case report
A sunday morning 34 years-old woman consulted the emergency department for of a fatigue and diarrhea. She reported a 7 kg weight-loss in the late 2 months associated with a lack of appetit. Her blood pressure 96/56 mmHg. Biologic assessment showed a natremia at the low range and a normal kaliemia. Hypoglycemia at 0.38 g/l was objectified. An acute adrenal insufficiency was suspected. Intravenous hydrocortisone and glucosed fluid infusion immediately after cortisol blood sample. The hormonal assesment confirmed a corticotrope insufficiency with a low level of both plasma cortisol 113 nmol/l (<138) and ACTH <0.2 nmol/l. Bacterial infection by Aeromonas punctata was confirmed. Oral antibiotic treatment using Ciprofloxacine 500 mg twice a day stoped diarrheas. Three months before, the patient reported an hemorrhagic delivery, a lack of lactation and persistance of amenorrhea. Other typical symptomes were also found: lack of pubic and axillairy pilosity and vaginal dryness. In this clinical context the diagnostic of SS was retained. A screening of other pituitary dysfunction showed, a thyreotrope insufficiency (low fT4 and fT3 with low normal TSH level), a low FSH and LH levels and low prolactinemia. IGF1 level was normal. After 48 h glucocorticoid substituition the patient presented a polyuric poludipsic (PUPD) syndrome. The fluid restriction test was rapidly stopped because of hypernatremia at 150 mmol/l. The treatment by desmopressin 90 µg/d was initiated with resolution of the PUPD syndrome and natremia normalisation. Pituitary MRI showed a sequelae-like changes involving the entire pituitary gland but respecting its stem. Post hypophyse was reduced to punctiform hyposignal T1. The diagnosis of central insipidus diabetes was confirmed.
Comments and conclusions
SS is due to a necrosis of the pituitary gland in the context of reduced brain output. Sometimes the diagnosis of this rare syndrome may be delayed notably when the first typical symptômes (lack of lactation, post-partum amenorrhea, lack of pubis hairs in the waxed women) are not spontanously reported by the patient. Acute adrenal gland insufficiency and even diabetes insipidus may occur lately with a severe clinical presentation in the course of common minor illness like bacterial diarrhea.

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EP751

Every post op hyponatremia is not a SIADH; missed case of hypopituitarism after TBI

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Introduction
The incidence of hospitalised and fatal traumatic brain injury(TBI) is 235/100 000 with an average mortality rate of 15/100 000. A meta-analysis from 19 studies showed a prevalence of hypopituitarism after TBI of 27.5%.
Case report
We report case of 72-year-old man, who suffered traumatic brain injury in October 2021, sustaining multiple skull fractures, with traumatic subarachnoid haemorrhage and subsequent pneumocephalus. He underwent burr-hole surgery with an extended stay on the neurosurgery ITU. After returning to ward, he started vomiting,became tachypnoeic,hypotensive and suffered a PEA cardiac arrest.ROSC was achieved and he was taken to ICU. During ITU stay he required adrenaline boluses followed by noradrenaline infusion to maintain his blood pressure. He was given stress dose of steroids during his subsequent ITU stay. He developed hyponatraemia that was attributed to SIADH, cortisol was not checked on admission. He was stepped down from ITU to ward and was noted to have postural hypotension and continuing hyponatraemia. He received a long acting steroid injection in knee for pseudogout and was manged with intravenous fluid and slow sodium tablets. He was discharged in February 2022 but developed ongoing symptoms-persistent tiredness and weight loss. His symptoms worsened in April 2022 when he presented to his GP with dizzy spells and was found to have postural hypotension and ongoing hyponatraemia. He was prescribed slow sodium tablets and fludrocortisone. He had a syncopal episode while on holiday and was admitted to hospital. He had hyponatraemia and was confused on admission. He subsequently underwent short Synacthen test and was diagnosed as having secondary adrenal insufficiency.He was then commenced on replacement hydrocortisone.A full pituitary hormone profile was completed. This showed evidence of secondary hypothyroidism and secondary hypogonadism. He was subsequently started on Levothyroxine and testosterone replacement, MRI pituitary showed partial pituitary damage with residual intact normal tissue.
Discussion
Pituitary dysfunction after TBI is a common complication. Postulated mechanisms of pathophysiology include primary injury caused by direct trauma and secondary involvement due to illness, hypotension and infarction. Unrecognised hypocotisolism related to pituitary dysfunction after TBI can be life threatening. In our patient, while he was inpatient had a long-acting steroid injection and stress-doses of steroid that may have temporarily protected him from symptoms of secondary adrenal insufficiency. His low sodium during admission was attributed to SIADH but secondary adrenal insufficiency should always be suspected in patients of TBI having hyponatraemia or/and hypotension.

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EP752

Response to quinagolide of a pituitary prolactin macroadenoma

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Introduction
The treatment of prolactin adenomas is medical based on the use of dopaminergic agonists but the presence of an underlying valvulopathy makes the treatment by cabergoline delicate.
Clinical case
We report the case of a 60 year old female patient, operated on for aortic valve disease, with moderate mitral leakage. On the occasion of a decrease in visual acuity; a prolactin macro adenoma is diagnosed In agreement with the cardiologist; we opt for a treatment with quinagolide at progressive dose leading to a decrease of prolactin with especially an improvement of the visual disorders
Conclusion
The presence of valvulopathy in patients with prolactin macroadenoma may hinder the practitioner in his therapeutic choice; although it is considered less effective than cabergoline, quinagolide has allowed the decompression of the visual pathways and remains an alternative in valvulopathic patients at risk.

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EP753

Double functional pituitary adenomas causing acromegaly and subclinical Cushing disease

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Introduction
Double Pituitary adenomas with growth hormone (GH) and adrenocorticotropic hormone (ACTH) secretion are very rare. They are responsible for acromegaly with hypercortisolism. Subclinical corticotropic adenomas are exceptional. Herein, we report the case of a patient with double functional pituitary adenomas causing acromegaly and subclinical Cushing's disease.
Observation
A 45-year-old woman was referred to our department for suspected acromegaly. Her past medical history included well-controlled diabetes mellitus treated with oral antidiabetic drugs and hypertension. On physical examination, she had a body weight of 65 kg, a body mass index of 26.7 kg/m^2, a blood pressure of 130/80 mmHg, a heart rate of 72 beats/min, enlarged hands and feet, a large prominent forehead, thickened lips, increased interdental spacing, and prognathism. No signs of hypercortisolism were found. Biological investigations showed an elevated insulin-like growth factor-1 (IGF-1) level at 555 ng/ml (normal range: 81–267), a GH nadir after 75 g oral glucose tolerance test at 2 ng/ml, a morning cortisol level at 158 ng/ml, an ACTH level at 64 pg/ml, a TSH level at 2.26 mIU/l (nr: 0.35–4.94), and a FT4 level at 12.8 pmol/l (nr: 10.6–19.4). Cortisol after the dexamethasone 4 mg suppression test was 86 ng/ml. The diagnosis of acromegaly associated with Cushing's disease was established. Pituitary magnetic resonance imaging (MRI) showed a pituitary macroadenoma with no clear limits, with heterogeneous signals before and after Gadolinium injection. The patient underwent transsphenoidal tumor resection. The pathological examination revealed two separate pituitary adenomas showing different histological, immunohistochemical, and ultrastructural features. The positivity to ACTH and GH was 100% and 80%, respectively.
Conclusion
This case emphasizes the necessity of an evaluation of all the pituitary axes in case of adenoma in order not to miss a double hormonal secretion or more even in the absence of suggestive clinical signs.

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EP754

Isolated hypopituitarism as the first manifestation of neurosarcoidosis

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Introduction
Sarcoidosis may affect the central and peripheral nervous systems in 5–16% of patients. In most cases, such involvement occurs within a multi-systemic disease. Neurological involvement is rare but a potentially life-threatening form of sarcoidosis. The endocrine manifestations of neurosarcoidosis include hypothalamic dysfunction, diabetes insipidus, hypopituitarism, and amenorrhea–galactorrhea syndrome. Herein, we report the case of a patient with hypopituitarism secondary to neurosarcoidosis with no other manifestations of the disease.
Observation
A 35-year-old man was admitted for severe hyponatremia. His past medical history was unremarkable. The diagnosis of acute hypopituitarism with ACTH and TSH deficiencies was established. The patient was put on hydrocortisone and then levothyroxine. Initial pituitary magnetic resonance imaging (MRI) revealed a thickened pituitary stalk, an ectopic posterior lobe, and an intrasellar process. The second MRI performed 18 days later, showed pituitary necrosis and a partially empty sella with optic chiasm ptosis. Biological tests were normal (total calcium level, protein electrophoresis, serum angiotensin-converting enzyme (ACE) level). Tuberculin skin test showed tuberculin anergy. Direct staining and culture do not demonstrate the presence of mycobacteria in urine and sputum. Chest-x-ray and cervical-thoracic-abdominal-pelvic computed tomography scan were normal. Bronchoalveolar lavage and salivary gland biopsy were normal. Immunological investigations revealed the presence of atypical ANCA, normal IgG4 levels, and negative AAN. Cerebrospinal fluid examination showed an increased ACE level. The diagnosis of neurosarcoidosis was established and the patient was treated with high-dose oral corticosteroids.
Conclusion
Our case represents an unusual form of neurosarcoidosis. It should then be considered as part of the etiological diagnosis in patients with hypopituitarism especially when infiltrative lesions of the infundibulum, hypothalamus, or pituitary gland are identified.

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EP755

Cushing's disease with empty sella turcica: A problematic situation

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Introduction
Cushing's disease is characterized by an endogenous hypercortisolism related to a pituitary adenoma, its association with an empty sella turcica is exceptionally rare.
Case report
A 55 year old diabetic patient with hypertension was admitted for investigation of Cushing's syndrome. Clinical examination found facial and truncal obesity with facial erythrosis, capillary fragility with multiple ecchymoses, proximal amyotrophy of the limbs. Biologically, urinary free cortisol was 5 times the normal range, midnight cortisol was elevated to 180 ng/ml and Adrenocorticotropic Hormone (ACTH) was 91 pg/ml confirming the ACTH-dependent nature of Cushing's syndrome, the high-dose dexamethasone suppression test was positive. Magnetic resonance imaging revealed an intra sellar arachnoidocele with no detectable adenoma. The diagnosis of cushing's disease was retained and the patient was put on ketoconazole 400 mg/d.
Discussion
Imaging-negative cushing's disease is not uncommon, the association with an empty sella turcica is a major challenge and could be explained by the apoplexy of a pituitary adenoma. Catheterization of the petrous sinuses remains the gold standard for topographic diagnosis. Transsphenoidal surgery is the first-line treatment but is not without risks. Medical treatment allows control of hypercortisolism in case of failure of surgery or while waiting for the appearance of an adenoma on imaging.
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EP756

Intrasellar ectopic salivary gland rests related with Rathke's cleft cyst

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Introductıon
Rathke's cleft cysts (RCCs) are benign lesions originating from the epithelial remnants of Rathke's pouch with a peak incidence at 30–50 years of age. It is detected at a rate of 13–33% in several autopsy series. RCC is usually asymptomatic and diagnosed incidentally. In symptomatic cases, common symptoms are headache, visual disturbance, and symptoms related to hypopituitarism.
Case
A 28-year-old male patient presented a three-year history of headaches, severe weakness, impotence, and decreased libido. The patient had no polyuria or polydipsia. Physical examination was unremarkable. Laboratory data revealed panhypopituitarism. TSH: 0.01 mIU/ml (0.27–4.2 mIU/ml), T4: 0.5 ng/dl (0.93–1.70 ng/dl), kortizol: 2, ACTH:13 pg/ml (7.2–63.3 pg/ml), FSH: 1 mIU/ml (1.1–12.4 mIU/ml), LH:1.1 mIU/ml (1.7–8.6 mIU/ml), total testosterone: <0.025 ng/ml (2.8–8) Prolactin: 2.72 ng/ml (4–15 ng/ml). MRI showed a cystic tumor in the sellar region, with a largest diameter of 11 mm. Replacement treatment with levothyroxine, hydrocortisone, and testosterone was initiated, and surgery was recommended because of panhypopituitarism. He underwent transsphenoidal surgery. His pathology is Rathke cleft cyst, and focal nonproliferative salivary gland glandular structures adjacent to these areas are observed.
Discussion
Pituitary development begins in the 3rd and 4th weeks of the fetal period. The anterior lobe (adenohypophysis) is derived from oral ectoderm and is epithelial in origin, whereas the posterior lobe (neurohypophysis) derives from the neural ectoderm. Rathke's cleft cysts originate from epithelial cells of the developing Rathke's pouch. It can be explained by the migration of seromucous glands located in the primitive oral cavity into the Rathke pouch. Salivary gland (SG) tissue may occur in different sites. Intrasellar ectopic SG rests are typically localized close to the neurohypophysis or in the pars intermedia, often communicating with the Rathke's cleft, and maybe incidentally found at autopsy. Only a small group of people is noticeable because of mass effects and endocrine dysfunction, particularly hyperprolactinemia, as the current literature is limited to case reports.

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EP757

A dwarfism revealing a Pituitary stalk interruption syndrome (PSIS) at the age of 36 years

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Introduction
Pituitary stalk interruption syndrome (PSIS) is a distinct developmental defect characterized by a thin or absent pituitary stalk, hypoplasia of the adenohypophysis, and ectopic location of the neurohypophysis.
Case report
A 36 years old male patient, full term born by vaginal delivery, with birth asphyxia. Birth weight was 2800 g, length was 51 cm, and no other postnatal events were noticed. Psychomotor milestones were achieved normally. his height remained at -4, -5 S.D. till this thirties. The clinical examination finds particular facial features with central adiposity. MRI hypothalamo hypophysia was performed showing ectopic posterior pituitary located adjacent to the optic chiasm, absent pituitary stalk, and severe anterior pituitary hypoplasia associated to type 1 chiari malformation. Hormonologic assessment showed an hypopituitarism.The patient was put on L-thyroxine, hyrocortisone and testosterone treatment.
Discussion
PSIS is manifested as isolated or combined pituitary hormone deficiencies (CPHDs) with variable timing in the onset of symptoms. The precise etiology of PSIS still remains elusive or incompletely confirmed in most cases. Adverse perinatal events, including breech delivery and hypoxia, were initially proposed as the underlying mechanism affecting the hypothalamic–pituitary axis. Nevertheless, recent findings have uncovered a wide variety of PSIS-associated molecular defects in genes involved in pituitary development. Severe and life-threatening symptomatology is observed in a subset of patients with complete pituitary hormone deficiency during the neonatal period. Nevertheless, most patients are referred later for growth retardation. Prompt and appropriate hormone substitution therapy constitutes the cornerstone of treatment.
Conclusion
PSIS is a developmental defect easily diagnosed by MRI, his diagnosis is often delayed, which often result in a gradual occurrence of multiple pituitary hormones deficiencies, requiring careful follow up of affected patients.
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EP758

Pituitary apoplexy in cabergoline-resistant macroprolactinoma

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Introduction
Pituitary apoplexy is a life-threatening clinical syndrome that develops as a result of bleeding or infarction in a pituitary adenoma. Here, we aimed to present a case of cabergoline-resistant macroprolactinoma who developed pituitary apoplexy.
Case Report
A 40-year-old male patient presented to neurology 2 years ago with severe headache. Brain magnetic resonance imaging (MRI) revealed a $15.5\times18\times21$ mm macroadenoma in the pituitary gland that did not compress the optic chiasm. Visual field examination was normal. He had loss of libido and erectile dysfunction. Endocrinological evaluation (Table 1) showed hyperprolactinemia and hypogonadism. With the diagnosis of macroprolactinoma, cabergoline 0.5 mg/week was started and it was planned to increase the dose gradually. He was informed about the side effects of cabergoline and the findings of pituitary apoplexy. After 3 months of treatment, the adenoma size was the same, but his complaints decreased, prolactin and testosterone were normal. Thereupon, the dose of cabergoline was increased to 3 mg/week. In the pituitary MRI performed at the end of 1 year, it was observed that the size of the adenoma remained constant, but the clinical and laboratory well-being continued. Adenoma-reducing transsphenoidal surgery was recommended for cabergoline-resistant macroprolactinoma. However, the patient did not accept surgical treatment. Six months later, he presented with severe headache, nausea, vomiting, weakness and blurred vision. Prolactin, cortisol, and testosterone levels were low (Table 1). Pituitary MRI revealed an increase in size of the adenoma and compression on the optic chiasm. Pituitary apoplexy and hypopituitarism were considered. No underlying predisposing factor was detected except for cabergoline use. Steroid replacement was started, adenoma resection was performed by transsphenoidal surgery and histologically confirmed as lactotroph adenoma. Visual field examination was normal in the postoperative follow-up, but hypopituitarism persisted.
Conclusion
Pituitary apoplexy due to the use of dopamine agonists in macroprolactinoma is a rare complication. Because of the high mortality and morbidity rate of pituitary apoplexy, it should be known that patients with macroprolactinoma should be followed closely while using dopamine agonists. It should be kept in mind that when pituitary apoplexy occurs, timely surgical decompression should be the best treatment option for patients.

Table 1: Laboratory findings

Parameter		Result	Reference Range
	First diagnosis	18th month	
Prolactin (μg/l)	>200	<0,25	2,64–13,13
Diluted prolactin (μg/l)	3652		2,64–13,13
Follicle Stimulating Hormone (IU/l)	2,21	3,38	1,27–19,26
Luteinizing Hormone (IU/l)	1,39	0,97	1,24–8,62
Total Testosterone (μg/l)	0,97	<0,1	1,98–6,79
Cortisol (μg/dl)	14,3	1,91	
Adrenocorticotrophic Hormone (ng/l)	27,9	18,4	<46

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EP759

Endocrinopathy behind the facemask – follow up

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A 44-year-old gentleman presented to the Emergency Department with a 2-week history of fever and rigors. Past medical history was unremarkable other than an earlier diagnosis of hypertension. He was noted to have new onset atrial fibrillation with rapid ventricular response; a diagnosis of hypertrophic obstructive cardiomyopathy (HOCM) was made on echocardiography. In addition, a vegetation was identified on the mitral valve. Treatment for infective endocarditis (*Streptococcus oralis*) was initiated and he was subsequently transferred to a specialist centre for mechanical mitral valve replacement surgery. Warfarin was commenced post operatively with target INR of 3.5–4.5. During the admission, a history of chronic headaches was investigated. MRI pituitary revealed a 3.8×1.9 cm macroadenoma with suprasellar extension and invasion of the right cavernous sinus. He was further evaluated in the outpatient endocrine clinic. On removal of his facemask, examination revealed typical acromegalic features with supraorbital ridge prominence, significant underbite and macroglossia. Visual fields were normal to confrontation testing. Pituitary function showed: IGF-1 140.3 nmol/l (range 8.5–31.0), 0900 h cortisol 352 nmol/l (range 200–750), prolactin 1119 mU/l (range 60–300), TSH 1.98 mU/l (range 0.34–5.60), FSH < 0.U/l (range 1.7–8.0), testosterone 8.7 (range 10.0–30.0). Acromegaly was confirmed with an oral glucose tolerance test. The patient was subsequently discussed in Pituitary MDT and commenced on monthly Lanreotide injections to induce tumor size reduction while awaiting pituitary surgery. His IGF-1 remained high despite monthly Lanreotide and therefore Cabergoline was added for further medical management whilst planning his surgery, since this required close collaboration with his cardiothoracic team regarding his cardiac function and prosthetic valve in addition to extensive discussions with Haematology regarding plans for safe peri-operative anticogulation. He underwent successful transphenoidal pituitary surgery; subsequent MRI imaging revealed a good surgical resection with histology confirming a sparsely granulated somatotroph pituitary adenoma (Ki67 1%). Despite a good surgical outcome, his post-operative course was complicated by repeated episodes of epistaxis requiring regular input from Haematology and ENT teams. Anticogulation was cautiously continued due to the high risk of mechanical valve related thrombosis. Control of epistaxis was eventually achieved following a return to theatre for ligation of the sphenopalatine artery. He was discharged once INR was within the therapeutic target range. This case highlights the requirement for early diagnosis and treatment to prevent further complications as well as the need for individualisation of complex treatment decisions through the involvement of multiple specialties within multi-disciplinary team working patterns.

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EP760

Recurrence of ACTH dependent Cushing's syndrome after pregnancy: Clinical case

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Introduction
Pituitary ACTH-dependent Cushing's syndrome (CS) is a condition characterized by an overproduction of cortisol due to pituitary adenoma which infers high morbidity and mortality. Transsphenoidal surgery (TSS) is the first-line therapy of an ACTH-secreting pituitary adenoma. But, even after surgical resection of the adenoma, up to 50% of cases may develop a recurrence of the disease.
Case presentation
A woman, 32 year-old, developed recurrent Cushing's disease after 6 years remission following TSS for a pituitary microadenoma. The first clinical symptoms appeared at the age of 26 after the pregnancy and birth (cycle disorder, obesity, weight gain by 15 kg, depression). According to medical history: mean 24-hour UFC was 652 719 ng/24 h, Serum cortisol was not suppressed after low-dose dexamethasone suppression testing (191 ng/ml), but was suppressed (28.3 ng/ml) during high-dose dexamethasone testing, Cortisol stimulation after CRF 225 ng/ml basally, maximum 284 ng/ml, ACTH 56.2 pg/ml, after CRF 112 pg/ml, respectively. These results suggested ACTH-dependent CS, underwent TSS. Histopathologic examination confirmed the diagnosis of pituitary adenoma with positive ACTH immunostaining. In the postoperative period there was clinical and laboratory remission, symptoms regressed, weight decreased. She got pregnant in a 2 and 5 years after the surgery, which ended with term deliveries, without complications. A year later, in the postpartum period, clinical signs of hypercortisolism accompanied moon face, and buffalo hump without purple striae, increased weight gain of 10 kg, headaches, and depression. Clinical examination revealed central obesity, moon face, body mass index (BMI) 29.7 kg/m^2, BP 150/90 mm Hg. A laboratory analysis showed: morning serum cortisol was 530 nmol/l (normal: 171–536 nmol/l), late-night salivary cortisol (LNSC) – 23.1 nmol/l (ref less than 7.56 nmol/l); plasma ACTH was 73.01 pg/ml (normal: 7.2–63.30 pg/ml). Persistent hypercortisolism continued for 7 years. MRI pituitary: no signs of adenoma, but recurrence of ACTH-dependent Cushing's syndrome was confirmed by CRH stimulation test, inferior petrosal sinus sampling (IPSS) and transnasal adenomectomy was performed. Histopathological examination – micro-adenoma with positive ACTH immunostaining. In the postoperative period no signs of Cushing.
Conclusion
In this case, pregnancy was a factor of debut and a recurrence of ACTH dependent Cushing's syndrome.

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EP761

Delayed onset of pasireotide-induced hyperglycemia: Report of two cases

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Introduction
Pasireotide is a potent somatostatin analogue (SSA) and used in therapy-refractory acromegaly, commonly after failure of treatment with first-generation SSA. However, it may induce severe hyperglycemia, which usually occurs rapidly after initiation of therapy and in general gradually improves over time. We here present two cases of young male patients who developed severe pasireotide-induced hyperglycemia after several years of treatment.
Case 1
The patient was diagnosed with gigantism due to a growth hormone secreting pituitary macroadenoma at the age of 17 and received pituitary surgery one month after diagnosis. Due to residual tumor tissue the patient received medical treatment with a dopamine agonist and then octreotide. However, only partial biochemical control has been achieved. Additional Gamma-Knife radiosurgery 3 years after diagnosis did not result in biochemical control within the following years. Ultimately, the patient was started on pasireotide subcutaneously in a clinical trial 8 years after diagnosis and reached biochemical control within months. After two years therapy was switched to pasireotide LAR. Glycemic status remained stable during the first 3 years of pasireotide therapy, but then HbA1c and fasting plasma-glucose (FPG) levels quickly increased and we initiated antidiabetic treatment. Pasireotide was continued. Currently, he is on a combination therapy with metformin, sitagliptin, and repaglinide with acceptable glycemic status while maintaining biochemical remission.
Case 2
The diagnosis of acromegaly was established in a 27-year-old male presenting with acral enlargement, paresthesia of both hands, thickening of fingers, prognathism, and progressive asthenia. Transsphenoidal resection of a pituitary macroadenoma ensued quickly, but IGF-I levels remained equally elevated during the months following surgery. He was treated with lanreotide, almost achieving biochemical control but with persistent clinical signs of active disease. The patient was then started on pasireotide subcutaneously in a clinical trial achieving IGF-I levels below the upper limit of normal. After two years the treatment was switched to pasireotide LAR. Afterwards FPG steadily increased and after two further years antidiabetic treatment became necessary. After two more years FPG and HbA1c continued to rise. As the patient refused more intensive antidiabetic treatment pasireotide had to be stopped. Glycemic status returned to normal thereafter.
Conclusion
We present two cases of patients with acromegaly who developed severe hyperglycemia only after several years of pasireotide treatment. Therefore, long-term monitoring of glucose control is necessary in the follow-up of pasireotide treatment.

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EP762

Challenges in the management of prolactinomas: A case of partial resistance to high-dose cabergoline in a young male with an invasive giant prolactinoma

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Background
Giant prolactinomas are rare pituitary tumours larger than >40 mm in diameter, representing 2–3% of prolactin secreting tumours. Management is challenging especially in male patients, due to resistance to dopamine agonists (DA).
Methods
Clinical, hormonal and imaging evaluation and follow-up
Aim
To describe a case of partially resistant giant prolactinoma in a young male patient
Case report
A 17-years old adolescent with a 2 years history of progressive loss of vision and visual field defects (right eye blindness and left eye temporal hemianopia) presented following MRI identification of a 30×28×45 mm sellar mass, extending suprasellary, into the left cavernous sinus, compressing the left temporal cerebral lobe. Examination revealed left oculomotor palsy, delayed puberty (Tanner stage III), without other signs of hypopituitarism. Laboratory workup demonstrated severe hyperprolactinemia (6739.8 ng/ml), normal IGF1 and thyrotroph and gonadotrop insufficiency. Family history was negative for MEN1 and FIPA and hyperparathyroidism screening was negative. Our MDT considered surgery for rapid visual pathways decompression, but a 2 week course of cabergoline lead to significant improvement of vision and visual fields, obviating the need for surgery. Continued cabergoline in escalating doses produced a steady reduction of prolactinemia and further visual improvement and a great reduction in tumour size. The evolution was complicated by an episode of pituitary apoplexy and transient hypocortisolism, managed conservatively. Gradual testosterone replacement led to induction of puberty, accompanied by a plateauing of prolactinemia to 33.5 ng/ml, despite escalation of cabergoline to 8 mg/week. Prolactinemia showe no response to added anastrozole, and then began rising slowly. Tumour control was maintained. Initial and follow-up echocardiograms were unremarkable.
Conclusion
Our case illustrates partial biochemical resistance to high-dose DA, despite excellent tumour response. Anastrozole did not improve the biochemical response. We are closely monitoring the patient, who continues to have an excellent clinical status.

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EP763

A rare case of Cushing syndrome ectopic-ACTH

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Introduction
Malignant tumors, nevertheless, have been associated with extremely high circulating ACTH and cortisol levels, and short duration of symptoms of Cushing syndrome (CS) besides atypical clinical phenotype, when compared with pituitary-dependent Cushing. Identification of the source of ACTH can be challenging, as sometimes the primary lesion is not identified even after prolonged and repeated follow-up
Case report
A 33-year-old woman with a history of insulin-induced diabetes admitted to our department for suspicion of ACTH-dependent Cushing's syndrome held in front of: a Cushing's syndrome clinic, biological Cushing's syndrome, CLU: 2894 µg/24 h, minute braking: negative, cortisolemia 32.1 µg/dl, ACTH: 232 ng/l, CT scan of the adrenal glands in favor of moderate adrenal hyperplasia. MRI Pituiray without anomaly, strong negative braking. an Octreoscan objectified the presence of two thyroid nodules of hypodense generation moderately fixing the radiotracer, measuring respectively 1.9×1.2 cm on the right and 1.5×1.1 cm on the left. The focus intensely fixes the retrotracheal radiotracer and the right paravertebral retrotracer. tumor markers are negative. the patient was operated on for anopathy: thyroid nodular dystrophy, reactive lymphadenitis, a review of the anopathy with iminohistochemistry is requested results in progress. the patient comes to our training 1 month post-operative, the patient reports a regular cycle return, the clinical examination shows a disappearance of purple stretch marks and bruises. Control octreoscan shows the absence of signs in favor of a neuroendocrine tumor at the pleuro-pulmonary, digestive or thyroid level.
Discussion
Most primary endocrine tumors responsible for Ectopic ACTH syndrome (EAS) are located in the chest. Among all ACTH-secreting thoracic tumors, the most common, in a modern endocrine patient recruitment, are welldifferentiated NETs located in the bronchi (formerly called 'carcinoids') and these account for 20% to 40% of all cases of EAS in recent series. They can recur, especially after initial resection without systematic lymphadenectomy. 'Tumorlets' or diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, a precursor to carcinoid tumors and tumorlets, represent a particular bronchial NET type, being small These are mainly located in the chest and can mimic lung metastases. Thymic NETs are also an important cause of EAS due to thoracic tumors accounting for 5% to 10% of EATs, depending on the series.
Conclusion
ACTH-dependent Cushing syndrome due to ectopic ACTH production most of times is difficult to manage. The identification of the source of ACTH may take many years until final diagnosis.

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EP764

A very rare case of familial glucagonoma with renin co-secretion and hypokalemia in MEN1 multiple neoplasia

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Introduction
A glucagonoma is a rare neuroendocrine tumor that originates almost exclusively in the pancreas and probably accounts for 1% of all neuroendocrine tumors. MEN1[1] is characterized by the development of primary hyperparathyroidism (PHPT), pancreatic neuroendocrine tumors and pituitary adenomas.
Methods
We present the case of a 39-year-old female, with history of type 2 diabetes mellitus and hypokalemia[2] who presented to the "C.I Parhon" National Institute of Endocrinology with repeated low potassium levels in the last year. Endocrine tests showed secondary hyperaldosteronism (renin 341.8 pg/ml, aldosterone 371 pg/ml), primary normocalcemic hyperparathyroidism (PTH 584 pg/ml) and hyperprolactinemia (69.63 ng/ml). The serum potassium level was low (1.9–2.7 mEq/l), totally asymptomatic. Abdominal MRI revealed a pancreatic corporeal-caudal tumor (40/10 mm) with an appearance compatible with a neuroendocrine tumor, with secondary lymph node, liver determinations and bilateral adrenal tumors. Fine needle aspiration from the pancreatic tumor revealed atypical cells for a neuroendocrine tumor proliferation. Neuroendocrine tumor markers: Cromogranin A 1700 ng/ml, glucagon 1329 ng/l. Pituitary MRI: left pituitary adenoma 1.03/1.05 cm. Normal pituitary function. Radionuclide Technetium 99m SESTAMIBI scan was positive for left inferior parathyroid.
Results
Corporal-caudal splenopancreatectomy en bloc with partial left adrenalectomy and enucleoresection of cephalopancreatic exopthytic tumor was performed. The pathology and IHC examination certifies well-differentiated neuroendocrine tumor G1 pT3 pN1 pM1a and AE1-AE3 positive chromogranin and synaptophysin in the tumor, negative CD56 and Ki67 < 1%.Microwave ablation of liver tumor segment VII. Lanreotid autogel was started. Despite sustained increased PTH values, the calcium level was normal during the follow up for 4 years.
Conclusions
The renin co-secretion from a glucagonoma is a very rare combination, with only few cases reported in literature. The hypokaliemia is severe and may be corrected after tumor debulking and systemic therapy of metastatic disease, but the prognosis is poor. Another rare occurrence is normocalcemic primary hyperparathyroidism in MEN 1 syndrome.
Keywords: glucagonoma, hypokalemia, MEN 1, secondary hyperaldosteronism.
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EP765

'Needless needles': Can GH injections be prevented by treatment of deep vitamin D deficiency?

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Introduction
Growth hormone (GH) is not only important for growth during childhood. Also, for (young) adults, growth hormone is important for bone mass, muscle strength and metabolism. GH deficiency (GHD) is a condition that can cause a broad range of adult health issues, if left untreated. Therefore on one hand, it is important to confirm and treat GHD after transfer to adult care. On the other hand, the personal and financial burden of *unnecessary* growth hormone injections should be avoided. For this reason, adolescents with childhood onset GHD should be retested after reaching adult height.
Case presentation
We present a case of a 19-year-old non-obese Caucasian male who, due to isolated GHD, was treated with GH during childhood (needle-free system). After reaching adult height, GH treatment was stopped and the patient was re-tested for GHD after a washout period. GH peak after stimulation with GHRH-arginine was 5.5 µg/l, which is considered persistent GHD. When the paediatric endocrinologist wanted to restart GH, patient refused, as he had a fear of needles and the needle-free GH was no longer available. Therefore the shared decision was made that restarting GH would be evaluated after transfer to adult endocrinology. At the first appointment at the adult outpatient clinic it was noted that, apart from low serum IGF-1 levels, 25-OH vitamin D level was extremely low (<10 nmol/l). Knowing that the promoter of the *GH1* gene contains a vitamin D-responsive element, it was hypothesized that the low vitamin D levels might have contributed to low IGF-1 levels. After six months of vitamin D replacement and near-normalisation of 25-OH vitamin D (49 nmol/l, ref. 50–120 nmol/l), IGF-1 level had almost normalised (18.6 nmol/l, ref 19–66 nmol/l). Although GHRH arginine test will be repeated to definitively rule out GHD, it was remarkable that IGF-1 levels clearly increased after treatment of severe vitamin D deficiency. Especially in this patient with needle-fear, this could avoid a lot of stress.
Conclusion
In our patient with childhood onset GHD, IGF-1 levels nearly normalised after treatment of his severe vitamin D deficiency. Especially as fear of needles is common during the transition phase (20–50% in adolescents and 20–30% in young adults), it is worth reassessing IGF-1 levels after vitamin D supplementation, to avoid needless GH injections.
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EP766

Gaps in the long term post-treatment follow-up of pituitary tumors

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Objective
To study the spectrum of Pituitary tumours, their presentation, treatment and compliance with follow-up.
Methods
A mixed retrospective and prospective study was conducted at the Medicell Institute of Diabetes, Endocrinology and Metabolism (MIDEM) and Jinnah Postgraduate Medical Centre (JPMC) Karachi,Pakistan. All cases of pituitary tumours, were prospectively followed. Data regarding age, gender, duration of disease, symptoms, mode of treatment administered and compliance with the follow-up instructions was retrieved.
Results
A total of 173 patients were enrolled with a mean age of 36.4 ± 10.6 years. Female predominance was seen in our study 97 (56.1%). Of the 136 married patients, subfertility was seen in 48 (36.3%). Headache was observed in 164 (94.8%) of patients. Prolactinoma was the lead tumour comprising of 76 cases (43.9%), followed by non-secretory tumours 47 (27.2%), and acromegaly 43 (24.9%). Other rare disorders including Cushing's disease, craniopharyngioma and gonadotropinoma were also seen. Cabergoline was prescribed in 136 (78.6%) cases. Transsphenoidal surgery (TSS) was done in 74 (42.8%) of patients. Out of 97 female patients, 38 (39.2%) had persistent amenorrhea post-treatment, while this data was not available for 40 (41.2%) of these women, who were lost to follow-up. The difference between mean prolactin levels prior and after the treatment (1390.048 ± 2646.986 versus 116.360 ± 163.369) were found to be statistically significant $P<0.001$). Similarly, IGF-1 levels were significantly improved post treatment indicating tumour stability. Moreover, the level of mean FT4 post-treatment was 1.64, reflecting adequate replacement.
Conclusion
Majority of the patients had improvement post-treatment in pituitary tumour symptoms, including vision, headache and sexual function. Failure to attend for follow-up for tumour stability, control of excess hormone, and pituitary hormone replacement was seen in a large number of patients in this study. This requires careful consideration of different strategies to ensure better long term care in pituitary tumours.

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EP767

Autosomal dominant familial neurohypophyseal diabetes insipidus in three generations

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Introduction
Familial neurohypophysial diabetes insipidus (FNDI), an autosomal dominant disorder, comes in many forms that are differentiated by the inheritance pattern and the underlying genetic lesion. The disease is caused by mutations in the vasopressin-neurophysin 2-copeptin protein (AVP-NPII), in wolframin (WFS1) or in proprotein convertase subtilisin/kexin type 1 (PCSK1) genes.
Materials and methods
In this study, we report a case of familial neurohypophyseal DI in three generations; followed in unit of the endocrinology, diabetology, metabolic diseases and nutrition department of the Mohammed VI University Hospital of Marrakesh.
Results
This was a 45-year-old patient who had been suffering from polyuro-polydipsia syndrome since the age of 12, with daily urine volumes ranging from 8.0 to 15.0 l, but had not seen a doctor. The patient was born without complications and had normal puberty. In the family history, three other members of the patient's family have also had polypolypolydispic syndrome since adolescence, covering three generations, including the patient's mother, her younger sister and daughter. A water restriction test was performed but the patient did not tolerate it. We completed with the minirin test with a good clinical response: urine concentrated with a volume of 500 ml, and urinary osmolarity at H4 of 276.13 (Fig. 2). As presented in (Fig. 3), cranial MRI revealed a hypersignal region in the posterior pituitary lobe. Serum cortisol, thyroid function, and estrogen were all in the normal range The growth hormone (GH), insulin-like growth factor (IGF)-1 levels and the genetic testing were not performed due to limited financial resources. After treatment with oral desmopressin 60 µg two times daily was started, the symptoms of polydipsia and polyuria were satisfactorily controlled. She currently drinks about 1.5 l of water per day and she has a urine volume of 1.5 l per day. Her sister's daily water/diuresis intake is 3.0 l/2.0 l, due to the effects of the medication.
Discussion
The mutations involved in familial neurophyphyseal DI include small deletions, as well as missense and nonsense mutations that affect the signal peptide, the AVP moiety, or the AVP carrier protein, NPII.
Conclusion
Familial neurohypophyseal ID is a rare hereditary disease that has a negative impact on the patient's quality of life. The majority of cases are inherited in an autosomal dominant pattern, which is why screening and appropriate management are necessary.

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EP768

Pituitary spindle cell oncocytoma presented as pituitary apoplexy, case study

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Introduction
Spindle cell oncocytoma (SCO) of the pituitary gland is a rare thyroid transcription factor 1 (TTF-1)-positive pituitary neoplasm.

Observation
We report the case of a 42-year-old man, with a personal history of type 2 diabetes, consulting for intense headaches and vomiting. The visual field shows an amputation of the left temporal hemifield and the MRI shows a pituitary adenoma with suprasellar development, initially measuring 22×28×37 mm, taking contrast heterogeneously and presence of hemorrhagic areas. The biological assessment objectified a normal level of prolactin and a triple deficit corticotrope, thyrotrope and gonadotrope. The diagnosis of pituitary apoplexy was retained. The patient received high-dose corticosteroid therapy. 20 days later, MRI showed a reduction in tumor volume measuring 22×17×21 mm with normalization of the visual field. The patient was put on 2 mg per week of cabergoline with regular monitoring. Two years later the MRI showed an increase in tumor volume 18×26×16.6 with bitemporal hemianopsia. The patient underwent transphenoidal surgery. The pathology concludes to a spindle cell oncocytoma of the hypophysis. Two months later, the visual field has not improved. The MRI shows an increase in the size of the lesion measuring 18×26×24 mm.
Discussion
SCO was first described by Roncaroli *et al*. in 2002, subsequently less than 100 cases have been described in the literature. Clinically, biologically and morphologically SCOs are indistinguishable from other sellar tumors. The usual presentation is that of an intracranial tumor syndrome associated with pan hypopituitarism. However, a recent data showed that frequent endocrine-related symptoms, hypervascular signs, and anterosuperior displacement of the gland support preoperative diagnosis of SCO. The tumor is classified in the WHO classification of tumors of the central nervous system from 2007 as grade I. It consists of spindle cells with eosinophilic, finely granular, mitochondria-rich cytoplasm, shows immunoreactivity to TTF-1, and lacks expression of chromogranin and pituitary hormones. Global tumor resection (GTR) seems to have better long-term tumor control, whereas the fibrous, hypervascular, and adhesive nature of SCO makes it difficult to achieve GTR. In patients with non-GTR, radiotherapy may help decrease tumor progression. In our case, we opted for revision surgery followed by radiotherapy.

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EP769

MRI assessment of typical pituitary gland size and shape: Age and gender associated changes

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Background
For a thorough evaluation of the pituitary gland, it is important to understand its typical structure, including the physiological differences in size and form across age groups in both males and females.
Objectives
To use magnetic resonance images to examine the size, shape, and average normal volume of the normal pituitary gland at various age groups in both genders (MRI).
Material and methods
200 individuals who underwent brain MRIs in the department were included in the retrospective analysis, with 161 men and 39 women, ages ranging from one year to 50 years. Patients with endocrine or pituitary disorders weren't allowed to participate in the study. MRI scanner was used to capture every MRI image. ANOVA and Chi-square tests were used to determine the relationship between mean volume and age. A P-value < 0.04 was regarded as significant.
Results
Female patients in each age group had pituitary glands that were on average more than male patients in the same age group. In the age range of 1–11 years, the average pituitary volume was 5.2 ± 1.3 mm. The average pituitary volume was measured at 6.2 ± 1.7 mm in the age groups of 20 to 31 years, 30–41 years, and 40–51 years. The most typical form was flat, which was seen in 45% of persons across all age groups and both genders, followed by convex in 31.1% and concave in 22.7%. Males had a mean pituitary volume of 209 ± 0.71 mm^3 while females had a mean pituitary volume of 199 ± 0.5 mm^3 in the age range of 1 to 11 years. The average pituitary volume in people between the ages of 11 and 20 was 341 ± 126 mm^3 in men and 281 ± 122 mm^3 in women. The mean pituitary volume in people aged 20–31 was 431 ± 115 mm^3 in men and 441 ± 181 mm^3 in women. Males had a mean pituitary volume of 381 ± 141 mm^3 and females had a mean pituitary volume of $441 \pm 110 \pm 115$ mm^3 in the 30- to 41-year age range. The average pituitary volume in those aged 41–50 was 421 ± 115 mm^3 in women and 401 ± 158 mm^3 in men.
Conclusion
To compare the abnormal growth in size, knowledge of physiological variation in the pituitary gland's size and form is required. Pituitary glands that are borderline abnormal in size and shape should have a dynamic contrast MRI examination performed to further assess them.

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EP770

Re-evaluation of MRI in the follow-up of acromegaly – a path towards long-term remission?

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Introduction
Remission by complete surgical tumour removal is not achieved in all patients with acromegaly and a subset of patients remain on long-term pharmacological treatment. Repeated surgery or targeted radiation therapy can be considered in patients with residual or recurrent tumour. Identification of residual or recurrent tumour available for surgical treatment can be challenging, and underreporting may lead to a loss in treatment opportunity. The aim of the present study was therefore to identify pituitary tumour remnants by systematic re-assessment of MRIs in pharmacologically treated patients with acromegaly.
Methods
Adult patients diagnosed and managed at a tertiary care centre 2005–2021 and presently on pharmacological treatment for acromegaly were included. Main outcome: Number and proportion of patients with a visible tumour, no visible tumour or a possible finding on MRI. A trained clinician (SA) and radiologist (MK) separately classified the latest routine MRI in a standardized manner, also taking into consideration baseline and all follow-up MRIs. In case of discrepant classification, consensus was achieved together with an experienced neuroradiologist (GR). Routine MRI reports were compared with the consensus classification.
Results
The study cohort consisted of 78 patients, of which 35 were women. Visible tumours and possible findings were seen in 31 (40%) and 36 (46%) patients, respectively. In 11 (14%) patients no visible tumours were seen. No visible tumours were reported in 23 (29%) patients in the routine MRI report, while we identified visible tumours in 2 (9%) and possible findings in 12 (52%) of the same 23 patients. Discrepancies between the routine reports and consensus classification were found in 31 (40%) patients.
Conclusion
Our study found visible tumours or possible findings in the majority of the patients. Identification of tumour remnants in patients with secretory activity is important as they may be candidates for redo surgery or targeted radiotherapy. Better imaging protocols or more advanced imaging may further contribute to tumour identification in uncertain findings.

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EP771

A rare case of macro-ACTH in patient with adrenal incidentaloma

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Introduction
Adrenocorticotropic hormone (ACTH) is a tropic hormone produced by the anterior pituitary that stimulates the adrenal glands to release cortisol. The ACTH measurement is often used to diagnose the pituitary and/or adrenal disorders, mainly Cushing's disease, Cushing's syndrome, Addison's disease and hypopituitarism. Therefore, the assessment of plasma ACTH concentration is a crucial step in the differential diagnosis of hypothalamic–pituitary–adrenal axis dysfunction. The purpose of our study was to present a case of patient with unexpectedly high concentration of ACTH

Case details
A 63-year-old Caucasian man was referred to our clinic for hormonal diagnostics due to a tumor in the left adrenal gland found in an abdominal CT scan, which showed an 11×10 mm mass with attenuation of approximately 20 HU (Hounsfield unit) in the left adrenal gland. Contrast-enhanced magnetic resonance imaging showed an 11×13 mm tumor without features of a lipid-rich adrenal adenoma. Plasma ACTH levels were highly elevated with normal cortisol levels using chemiluminescent immunoassay (Immulite 2000Xpi). The 24-hour ACTH and cortisol secretion profiles in the serum of the patients were respectively 602.00 [pg/ml] and 19.10 [μg/dl] at 0800 h, and 539.00 [pg/ml] and 3.12 [μg/dl] at 1000 h. Cushing's disease (due to an ACTH-secreting pituitary tumor) was ruled out by a low-dose dexamethasone suppression test, and Addison's disease (adrenal insufficiency) was ruled out by a normal Synacthenem short test. No pathological changes were found on MR imaging of the pituitary. In addition, polyethylene glycol 25% (PEG) precipitation and serial dilutions were applied to the serum. After PEG precipitation, ACTH decreased from 331 to 18.92 [pg/ml] (recovery: 5.72%). Endocrine diagnostics showed no hormonal activity of the adenoma in the left adrenal gland.
Conclusion
Macro-ACTH should be suspected when elevated ACTH levels are not consistent with clinical picture. Consideration of alternative testing methods, including PEG precipitation testing and clinical assessment, are of paramount importance in making the correct diagnosis. Strict cooperation between the physician and the laboratory is important in the approach to such cases.

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EP772

Characteristics of pituitary insufficiency in acromegaly: report on 28 cases

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Introduction
Acromegaly is a rare condition secondary to the hypersecretion of GH, often by a pituitary adenoma, which can lead to hypopituitarism of varying degrees. Our study aimed to analyze the characteristics of pituitary insufficiency during acromegaly and to search for its predictive factors.
Methods
Retrospective study carried out in the endocrinology department of Charles Nicolles Hospital. We recorded 28 patients with acromegaly over a period of 30 years.
Results
The study included 17 women and 11 men. The mean age at diagnosis of acromegaly was 45.9±13.9 years. Acromegaly was due to a pituitary adenoma in all cases (4 microadenomas and 24 macroadenomas). The average size of the adenomas was 20.4±9 mm. The hormonal assessment showed gonadotropic insufficiency, corticotropic insufficiency, and thyroid insufficiency in 67, 41, and 19% of cases. Thyroid insufficiency was present in 4 women and 1 man. The average size of the adenoma in the affected subjects was 24.8 mm. Gonadotropic insufficiency was present in 10 women and 8 men. The mean size of adenoma in these patients was 23.9±7, 8 mm with a statistically significant difference compared to the unaffected subjects 13, 8±8, 2 mm ($P=0.008$). GH nadir under OGTT ($P=0.03$) and tumor size ($P<10\text{-}3$) were significantly higher in patients with corticotropic insufficiency. A positive correlation was found between the number of affected axes with the value of GH nadir under HGPO75 ($r=0.611$; $P=0.001$) and the size of the adenoma ($r=0.744$; $P<10\text{-}3$). The number of affected axes was significantly higher in patients with aggressive adenoma ($P=0.031$). Age, gender and diagnostic delay did not significantly interfere with the number of pituitary deficient
Conclusion
We concluded that Tumor size, aggressive adenoma and GH nadir are a predictive factors of pituitary insufficiency.

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EP773

Metabolic profile during Sheehan's syndrome

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Introduction
– Sheehan syndrome (SS), or postpartum pituitary necrosis, is a rare but potentially serious complication of postpartum.
– SS remains an important cause of hypopituitarism in Morocco.
– The aim of this study is to evaluate the metabolic profile of patients with SS.
Materials and methods
– This is a retrospective descriptive study conducted in the endocrinology department, spread over a period of 12 years, between the year 2010 and 2022, The data were collected on a data sheet based on the analysis of medical records (paper and computer) and telephone calls if information was missing.
Results
– We collected 28 patients followed for Sheehan's syndrome during the study period from 2010 to 2022, The average age was 47±7 years with extremes ranging from 35 to 81 years, All patients explored had a thyroid insufficiency, Corticotropic insufficiency was found in 27 patients, Prolactinemia was low in 20 patients with a mean level of 2.6±1.65 ng/ml, 23 patients had a disturbed gonadotropic balance, The somatotropic axis was not explored in our patients, None of the patients had diabetes insipidus. The average BMI of the patients was 28 kg/m^2±4.89, and the average waist circumference was 95.7±4.34 cm, HTA in 3 patients, Five patients had a blood glucose level < 0.8 g/l. The rest of the patients had correct blood glucose levels. One case of diabetes mellitus revealed during the follow up, Hypercholesterolemia was found in 13 patients (46.42%). All patients had a pituitary MRI which revealed: an empty sella turcica in 15 patients, 1 case of anteropituitary hypotrophy.
Discussion
– The results of our study agree with those of the literature and show an overexposure to metabolic syndrome in patients with SS.
– This metabolic syndrome is related to the associated anteropituitary deficits:
– GH deficiency is associated with: Dyslipidemia, Obesity and body composition changes, and hypertension. Thyrotropic deficiency is associated with: HTA, An increase in total cholesterol, LDL, and triglyceridemia. The impact on HDL is more controversial.
– Gonadotropic deficiency is associated with: Change in body fat distribution from gynoid to android, Dyslipidemia, Disorder of carbohydrate metabolism, and HTA.
Conclusion
– Reduction of morbi-mortality associated with Sheehan syndrome relies on prevention and early diagnosis especially in our setting.
– GH deficiency seems to be at the center of the metabolic abnormalities observed in patients with hypopituitarism.

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EP774

The role of artificial intelligence algorithm in predicting the prognosis in prolactinomas

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Objective
To test the utility of the artificial learning algorithms using magnetic resonance (MR) images of the pituitary gland in predicting the prognosis of prolactinoma.
Methods
This single-center, retrospective study was conducted in the Pituitary Center of a tertiary care university hospital. A total of 224 images derived from 38 patients with treatment-refractory prolactinoma, 23 patients with prolactinoma remission and 51 healthy individuals were used. Pituitary MRI protocols are of three sequences: T1-weighted imaging (T1WI), contrast-enhanced T1WI (CE-T1), and T2-weighted imaging (T2WI). A machine learning algorithm that includes image filtering and classification. Data were classified with support vector machine.
Results
No difference was found between the refractory and the remission groups in terms of age, sex, education, the baseline prolactin level and radiological features. Images were classified with a support vector machine; area under curve (AUC), accuracy rate, sensitivity and specificity of 0.90 (95% confidence interval, 0.679–1), 91.6%, 91.7%, 88.3%, respectively.
Conclusion
These results indicate that a new image of unknown nature can be correctly identified with the specified percentages.
ROC Curve

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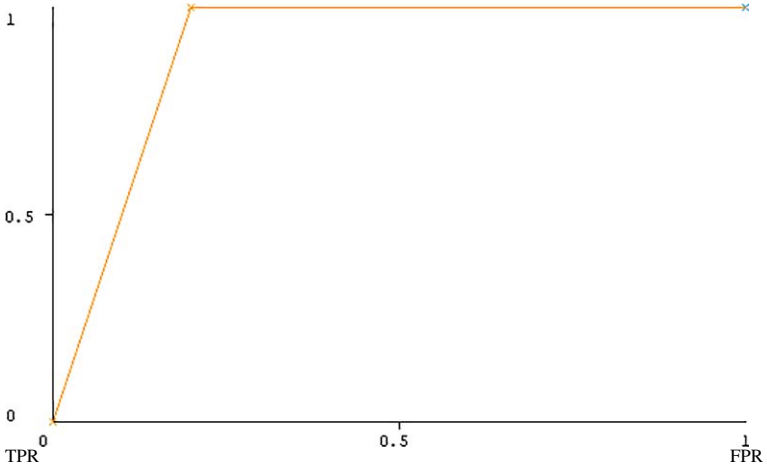
(Abstract EP774).



TPR: True Positive Rate
FPR: False Positive Rate

EP775

Quality of life in acromegaly

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Introduction
Acromegaly is a rare chronic disease characterized by systemic comorbidity. As a chronic disease, which in most cases requires long-term treatment, it is often accompanied by musculoskeletal, metabolic, and cardiovascular diseases, as well as headaches, anxiety, and depression, which leads to impaired quality of life.
Aim
Assessment of quality of life in patients with acromegaly compared to healthy controls.
Materials and methods
In the study participated 18 patients with active acromegaly (51.7±11.7 years, 38.9% men, 61.1% women) compared to 18 healthy individuals of similar age (48.9±11.5 years, 16.7% men, 83.3% women). Growth hormone in oral glucose tolerance test were determined as well as levels of IGF1. All participants filled out the SF36 quality of life questionnaire. Arithmetic mean±SD. and Mann–Withney test were used for statistical processing.
Results
We have shown that in the group of patients with acromegaly, IGF1 was elevated 2.53±1.1 times than ULN. 33.3% of patients had hypopituitarism. Examining 8 aspects of health within the SF36 questionnaire, the results showed that subjects with acromegaly had lower average values for each aspect, as well as the total score, compared to the control group, however statistics showed significant difference only in terms of general health (55.22±15.5 vs 75.00±13.3, $P<0.001$). There was statistically significant difference between the males and females in dimension A /physical functioning/ in favour of the males, which showed higher values (74.57±19.9 vs 55.00±22.0, $P<0.001$), in dimension B /mental health/ (73.71±15.5 vs 55.36±21.1, $P=0.004$), as well as in the total SF36 score (76.57±17.5 vs 56.64±21.5, $P<0.001$).
Conclusions
This is a pilot study in which it was found that patients with acromegaly had lower average results on SF36 questionnaire. Their perception of the general state of health was significantly impaired compared to the control group, which suggests poor quality of life. Further studies are needed to include larger acromegaly population as well as other assessment tests, in order to obtain relevant results and to gain complete insight into the quality of life of these patients.

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Features of neuroendocrine, hormonal and ophthalmic complications of giant pituitary adenomas depending on the volume and growth of the tumor (data from a prospective study)

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Aim
To study features of neuroendocrine, hormonal and ophthalmic complications of giant pituitary adenomas depending on the volume and growth of the tumor (data from a prospective study).
Material and methods
Us for the period from 2020 to 2022. 151 patients with macro- and giant NFPA were prospectively examined. According to the size of pituitary adenomas, patients of prospective (151 patients) observation were divided into 2 groups: group 1 – patients with macro NFPA – 55 persons, group 2 – patients with giant NFPA – 96 persons. The patients were subjected to a complete examination: biochemical, hormonal, immunocytochemical, ophthalmic neuroimaging (MRI of the pituitary gland). Some of investigations have been repeated in various time. MRI showed that in half of the cases pituitary adenomas were observed with a total growth variant – 104 cases (69.0%), as well as with endo- and suprasellar growth – 25 (16.5%)
Results
The most common complaint in patients with pituitary adenomas were: headaches – 122 patients (80.7%), bitemporal hemianopsia – 128 (84.7%) secondary amenorrhea – 51 patients out of 66 women (77.2%), decreased vision – 95 (62.8%), etc. It was found that in the 2nd group of patients, panhypopituitarism was most common – in 78 out of 96 patients (81.2%), postoperative panhypopituitarism occurred in 43 out of 96 patients (44.9%), while in group 1, panhypopituitarism was up to no operation was observed. Bitemporal hemianopsia was also observed with greater frequency in patients of group 2 – 93 cases (97%). In addition, secondary amenorrhea was also more common in patients of group 2 – 37 (38.5%). The most significant decrease in the average values of basal levels of tropic plasma hormones – STH, LH, FSH, ACTH – was recorded in patients of group 2. In addition, it was in these patients that the levels of cortisol and IGF-1 were also significantly reduced, while in patients of group 1, IGF-1 was on average within the normal range.
Conclusions
In general, patients had a decrease in the average values of tropic pituitary hormones, but most significantly and often in patients with giant pituitary adenomas. In patients with giant pituitary adenomas, first of all, there is a decrease in the level of growth hormone, FSH, LH (45%). The most pronounced neuroendocrine and ophthalmic disorders occurred in group 2 patients with giant pituitary adenomas.

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Differential diagnosis of the progressing pituitary lesion in a pregnant woman

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A 31-year-old female patient without previous history of pituitary diseases, at 16 weeks of 4th spontaneous pregnancy complained about severe headache; diplopia and right ptosis developed shortly, nausea and vomiting appeared. Brain MRI showed the mass lesion 30×19×14 mm (frontal×vertical×sagittal) with supralaterosellar extension, deforming and displacing optic chiasm; signs of pansinusitis, pathological contents of the right mastoid cells, vascular malformation in the right temporal lobe. Hormonal investigation showed low concentrations of TSH, free T4, free?3, cortisol and ACTH so hypopituitarism was diagnosed, and appropriate replacement therapy started. According to clinical symptoms, patient required higher doses of glucocorticosteroids to stop signs of adrenal insufficiency. She also received the antibiotic therapy and repeated surgical interventions due to purulent pansinusitis and secondary meningoencephalitis with the formation of an abscess of the left frontal lobe. However, the condition worsened despite the cavities and abscess sanitation: headaches persisted, a progressive decrease in vision (bilateral amaurosis) and bilateral ptosis were observed. Also poliuria up to 6–9 l/daily without hypernatremia or a decrease in the specific gravity of urine were revealed. An antidiuresis and hyponatremia 124 mmol/l were detected on the background of single-dose desmopressin 30 μg. Hyponatremia was self-recovered, however, low-normal values of sodium (130–135 mmol/l), potassium (3.6–4.3 mmol/l) and glucose (3.5–4.1 mmol/l) remained in dynamics. The MRI control every 2 weeks showed the rapid unexpectable growth of pituitary lesion with both cavernous sinus invasion: 47×21×18 mm – 60×24×21 mm (frontal×vertical×sagittal×). The diagnosis of pituitary adenoma was doubtful, the presence of hypophysitis or other sellar mass's etiology were assumed and pituitary biopsy was performed to clarify the diagnosis. The extranodal T/NK cell nasal lymphoma was diagnosed according to histological and immunohistochemical studies (Ki-67 up to 90%). Cesarean section was performed at 23 weeks of gestation for life indications to start chemotherapy. This clinical observation shows the difficulties of differential diagnosis of rare extranodal T/NK-cell lymphoma of the nasal type with CNS and pituitary lesion in a pregnant women with hypopituitarism and optic nerve atrophy. Such rude progression of pituitary lesion with predominant increase of frontal size is not characteristic for pituitary tumors and/or hypophysitis so rare and malignant disorders should be suspected.

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Induction of secondary sexual characteristics with gonadotropins in an adult male with Kallman syndrome

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Introduction
Hypogonadotropic hypogonadism is the cause of sexual deficiency, sometimes difficult to differentiate from constitutional growth delay (CGD).
Clinical case
A 19-year-old male consulting endocrinology for delayed puberty. Pointed to, at 13 years of age, as having had CGD. His medical report include a viral meningitis at 8 years of age and anosmia since 3 years of age. He expressed lack of sexual desire and concern about the size of his genitals. On physical examination, his weight was 64 kg, height 175 cm and his Tanner stage was II (A2P2G2). Suspecting Kallman syndrome (KS), due to delayed puberty and anosmia, the following tests were requested: bone age, which was 16 years old; bone mineral densitometry that diagnosed osteoporosis (*Z*-score −3.6 in the spine and −3.1 total femur); Pituitary MRI showing agenesis of bands and olfactory bulbs. Blood tests showed a normal pituitary hormonal profile, except for hypogonadotropic hypogonadism, low Inhibin-B and elevated Anti-Mullerian Hormone. A genetic study showed a mutation in the FGR1 gene (c.560G>A / p.Arg187His) associated with hypogonadism with or without anosmia, of autosomal dominant inheritance. His mother had the same mutation. With the diagnosis of KS, the different therapeutic options for the induction of secondary sexual characteristics were discussed: testosterone analogues or use of gonadotropins, opting for the second to also achieve gonad development. HCG 1000UI twice a week and rFSH 75UI 3 times a week were started, without side effects. After 8 months of treatment, rFSH was increased to 150UI. The clinical and analytical evolution was adequate, presenting a Tanner IV stage at 13 months and his first seminogram reported hypospermia. (Table 1)

Table 1

	Basal	3 months	7 months	13 months
FSH (mUI/ml)	0,7	1,1	2,8	4,6
LH (mUI/ml)	0,22	<0,12	<0,12	<0,12
Testosterone (ng/ml)	0,13	6,7	8,8	8,6
17-beta-estradiol (pg/ml)	<24	66	58	59
Inhibin-B (pg/ml)	58	74	71	90
Anti-Mullerian (ng/ml)	67,6	21,3	–	5,57
Testicles (cc)	3–4	5–6	6–7	12

Conclusions
Importance of early diagnosis and treatment of hypogonadotrophic hypogonadism in KS to perform adequate pubertal induction, achieve sexual and bone maturity, and avoid emotional and social problems. Gonadotropin therapy is an effective alternative to testosterone analogues for achieving induction of secondary sexual characteristics, testicular development and fertility.

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Mental health issues of patients with acromegaly: A systematic review

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Background
Acromegaly which is caused by excessive growth hormone is a rare chronicle endocrine disorder. Because it is a rare disorder, limited data are available on the impact and consequences of acromegaly on the mental health of patients, but the investigations are growing over time.
Aim
It aims to summarize the evidence identifying the mental health issues of patients with acromegaly.
Methods
MEDLINE (PubMed), Web of Science, and CINAHL databases were searched to retrieve potential studies from January 2000 to December 2022. Two reviewers independently screened abstracts, following specific eligibility criteria.
Findings
According to the studies, the main mental health issue was decreasing the quality of life of the patients. Other mental health issues were having depressive symptoms and mood swings, feeling of burden, impairments in body-self-perception, disruption in interpersonal relations, decrease in sleep quality, and social withdrawal anxiety.
Conclusion
Overall, the findings of this review suggest that there are many different mental health issues among patients with acromegaly which emphasize holistic health care. Also, the number of psychological interventional randomized controlled studies should be increased.

Keywords: acromegaly, mental health, quality of life
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Gelastic seizures caused by pituitary stalk interruption syndrome: Case report

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Introduction
Gelastic seizures have been typically described with hypothalamic hamartomas and precocious puberty. Invasive EEG recordings have shown that gelastic seizures originated from the hypothalamic hamartomas, however recent findings

have shown that they might also arise from other central lesions, like tumors, malformations of cortical development, postinfectious foci and other hypotalamic or pituitary abnormalities. In this case, we describe a patient with gelastic seizures and a short stature, in whom pituitary stalk interruption syndrome was discovered.
Case presentation
We report the case of a 13-year-old patient, who presented with slowed growth and short stature. Parents described brief laughter attacks, apparently unmotivated, that was perceived as strange behavior by his family. Physical examination showed a height of 142 cm which was below the second percentile for chronological age, and weight was 50 kg which was normal for age. Bone age was at 12 years. EEG showed some rare focal frontal lobe discharges. Laboratory findings revealed hypopituitarism with a thyroid-stimulating hormone level of 2.7 mIU/l and free thyroxine at 7.8 pmol/l (normal range 11 to 18 pmol/l). Cortisol level was 196 and 188 nmol/l after ACTH stimulation test. The rest of the biological investigation was normal. The patient underwent Insulin-induced hypoglycemia test and Glucagon stimulation test. Both tests confirmed the diagnosis of growth hormone deficiency since the maximal level of GH was 0.65 mI/l. Combined pituitary hormone deficiency was therefore held. Imaging of the sellar region was conducted, showing the typical triad of pituitary stalk interruption syndrome with interrupted pituitary stalk, hypoplasia of the anterior pituitary and ectopic posterior pituitary. Patient was treated with lamotrigin, risperidone, hydrocortisone and levothyroxin, and received growth hormone replacement therapy with good statural evolution. Puberty was induced at the age of 19 with good response.
Conclusion
These findings suggest that gelastic seizures can be generated in the hypothalamus or in its neighboring regions. Patients who suffer from these seizures should be screened for central endocrine abnormalities including precocious puberty and hypopituitarism.

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EP781

Macroprolactinoma in a patient with Schizophrenia: which illness should be treated first?

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Introduction
Prolactinomas are the most common of functional pituitary tumors. Dopamine agonists are the first line treatment of prolactinomas but have antagonistic effect with antipsychotics (dopamine receptor blockers) used in schizophrenia. The association between these two illnesses is a medical challenge, as the treatment of one disease can exacerbate the symptoms of the other one.
Clinical case
We report the case of a 72-year old man, newly diagnosed with schizophrenia (in March 2022) on the basis of positive symptoms. After two months of daily treatment (dopamine receptor blockers) the patient presented frequent headache. The MRI revealed a pituitary macroadenoma ($20 \times 15 \times 18$ mm) with cavernous sinus invasion without displacement of the optic chiasma. Hormonal evaluation revealed elevated serum prolactin levels at 4237.29 mUI/l. The other pituitary hormones were normal. The patient was initially treated with 1.5 mg/week of Cabergoline. Two months later, serum prolactin levels were reduced down to 1250 mUI/l. However, the patient developed episodes of visual hallucinations: zoophilia. The decision was to adjust his antipsychotic treatment by adding haloperidol and to reduce the dose of cabergoline down to 0.5 mg/week. The following month was marked by the increase in serum prolactin levels up to 1500 mUI/l with no progression of the macroadenoma showed on MRI and with stabilization of schizophrenia positive symptoms.
Conclusion
Treating a patient with both schizophrenia and macroprolactinoma is a balance between both entities: symptoms and treatment's side effects. We should monitor the treatment doses to avoid their side effects and exacerbation of chronic diseases.

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Prolactinoma in women

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Introduction
Prolactinoma is the most common type of pituitary adenoma, but it still presents difficulties in management especially in women who present some particularities hence the interest of our study.[1]
Material and method
This is a retrospective, descriptive study including 14 patients, hospitalized in the Endocrinology-Diabetology-Nutrition Department at CHU-Mohammed-VI-Oujda, between 2016–2022. The statistical analysis was performed by SPSS version 21 software.
Results
The mean age of the patients was 35.9 ± 13.2 years, of which 55.5% were in the menopausal period. The mode of revelation was mainly presented by a tumor syndrome in 57.1% of cases, isolated signs of hyperprolactinemia in 42.9%, while infertility was observed in 35.7%. Galactorrhea was present in 64.3% of women, cycle disorders in 78.6%, and decreased libido in 28.6%. The mean prolactin level was 353.4 ng/ml, associated with a gonadotropic deficit in 64.3%. Morphologically, macroprolactinomas predominated with 57.1% of cases. All patients benefited from medical treatment with dopaminergic agonists, and surgery in 21% of cases, which allowed recovery of gonadotropic function in 85% of cases, and the achievement of pregnancy in 28.5% of cases.
Discussion-conclusion
Dopaminergic agonists remain the effective first-line treatment for prolactinomas, allowing both the restoration of gonadal function and the achievement of pregnancy, which remains however of delicate management requiring a codified management[2].
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Radiological features of non-functioning pituitary adenomas in the Tunisian population

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Objective
To describe the radiological features of non-functioning pituitary adenomas (NFPA) at diagnosis.
Patients and methods
A retrospective descriptive study of 35 patients followed for NFPA between 2000 and 2022. A pituitary magnetic resonance imaging (MRI) scan was performed in all patients.
Results
The mean age was 52.1 ± 11.4 years with a male predominance (61.3%). Pituitary tumor syndrome was the main reason for consultation (77.4%). Visual impairments were observed in 80.6% of cases. It was frequently a macroadenoma in 90%, and a microadenoma in 10%. The majority of tumors were between 1 and 2 cm in size (46.7%). In 10% of the cases, the NFPAs were larger than 4 cm in diameter. Radiological analysis revealed hemorrhagic lesions in 25% of cases, and rarely a necrotic aspect (19.2%). Optic structures were invaded in 41.4%. Sphenoidal sinus infiltration was observed in 32.1%. In two-thirds of the cases, the cavernous sinus was invaded, indicating a locally advanced tumor status. The NFPA showed an aspect encompassing the internal carotid artery partially ($< 180°$) in 53.3% and massively ($> 180°$) in 13.3% of cases.
Discussion
The most common radiological findings at the time of diagnosis of NFPA are those of a locally aggressive sellar tumor invading the noble visual and vascular structures. This locoregional aggressiveness poses a therapeutic challenge, particularly for surgical resection, which is often incomplete. The tumor residue is a major prognostic factor that requires clinical, ophthalmological, and radiological monitoring, sometimes with adjuvant treatment (radiotherapy, surgical revision).
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EP784

Cushing's disease with negative imaging: What diagnostic and therapeutic approach?

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Introduction
Cushing's disease with negative hypothalamic–pituitary imaging is not a rare situation,since it is found in 1/3 of cases. This is a situation that complicates the etiological and therapeutic approach of the pathology, questioning the practitioner as to the effectiveness of pituitary surgery in this case.
Objective of the study
The aim of our study was to compare the results of pituitary surgery in the groups of patients with and without visualization of the adenoma on imaging and the contribution of petrous sinus catheterization in the latter.
Patients and methods
This is a retrospective study including 69 patients with Cushing's disease, over a period from January 1999 to August 2022, admitted to the endocrinology department of EPH Bologhine. Patients with exogenous Cushing's syndrome, ACTH-dependent Cushing's syndrome of paraneoplastic origin, and pseudo-Cushing's were excluded from the study. The statistical test used in this study is the T-student with P-value < 0.05 considered significant.
Results
Our series delivered 69 patients (55 women and 14 men) with Cushing's disease. 13 patients had a normal hypothalamic–pituitary MRI, ie 18.84% of cases, and 7 of them had undergone petrous sinus catheterization (53.84%). In 85.71% of cases, i.e. in 6 patients, catheterization revealed a centro-peripheral gradient, with lateralization of secretion in 57.14% of our patients (75% on the right and 25% on the left). Transsphenoidal surgery was the preferred approach in 6 of these patients (46.15%) with clinical and biological remission of Cushing's syndrome in 38% of cases in the group with normal hypothalamic–pituitary MRI, compared to 35.71% in patients with adenoma visualized on imaging (P-value = 0.046). Patients who did not obtain surgery were either lost to follow-up (6 patients) or died (1 case)
Conclusion
The etiological diagnosis of ACTH-dependent hypercorticism is not always easy. It turns out that in a third of the cases, the imaging techniques, as advanced as they are, do not make it possible to highlight the microadenoma in question. This is where catheterization of the petrous sinuses should provide the topographical diagnosis of Cushing's syndrome. In first intention, surgery via the transsphenoidal approach should be preferred. However, drug treatments remain important in the event of failure of surgery or while waiting for the appearance of a pituitary image.

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Acromegaly and metabolic comorbidities – a retrospective study

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Introduction
Acromegaly is a rare endocrine disease characterised by excess GH produced by a pituitary adenoma. It is associated with several complications and comorbidities. Metabolic alterations such as diabetes and dyslipidemia are quite frequent described in these patients.
Materials and methods
This is a retrospective observational cross-sectional study meant to assess the metabolic modifications in a group of acromegaly patients evaluated in our department.
Results
We included 67 patients in our study (38 female and 29 male). The mean age at diagnosis was 46.15 while mean disease duration was 10.42 years with 38 patients having below 10 years of disease activity. 77.6% of our patients presented with macroadenoma at diagnosis. There were 15 patients who refused surgery or had contraindication and 31 patients who did not undergo any type of radiotherapy. 42 patients received treatment at one point in time with a somatostatin analogue, 13 patients with pegvisomant and 26 patients with dopamine agonist. Out of all patients, 20 had no tumoral rest, no medical treatment and no disease activity (random GH $<$ 1 ng/ml, GH OGTT $<$ 0.4 ng/ml or GH/24 h $<$ 1 ng/ml, IGF1 $<$ 1.3$\times$ upper superior limit adjusted for sex and age), 24 were in biochemical remission and 23 still had active disease with partial response. Diabetes was diagnosed in 42 patients (22 female and 20 male) and dyslipidemia in 52 patients (30 female and 22 male). People with more than 10 years of disease activity had higher IGF1/USL in female patients, higher glycemia in male patients and higher triglycerides with lower HDL cholesterol irrespective of sex. Diabetic patients had higher mean value for GH over 24 h and IGF1/USL compared to those without diabetes, irrespective of sex and irrespective of disease status (complete, biochemical or partial response). Female patients with dyslipidemia had higher mean value for GH over 24 h and IGF1/USL. Female patients presented higher IGF1/USL than men in both diabetic and dyslipidemic groups. In both diabetic and dyslipidemic groups, higher values of GH/24 h and IGF1/USL were correlated with higher glycemia ($P > 0.05$) and triglycerides ($P < 0.05$).
Conclusions
Acromegaly is a complex pathology and needs to be treated accordingly. Diabetes and dyslipidemia are important complications which do not need to be overlooked and could be linked to disease activity.

Key words: acromegaly, diabetes, dyslipidemia, retrospective study
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De-escalation treatment with pasireotide for aggressive acromegaly: A long-term experience

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Introduction
Pasireotide long acting release (LAR) is approved for second line treatment of acromegaly. We present 3 patients with aggressive acromegaly treated with a personalized de-escalation approach.
Case 1
A 61-year-old female affected by acromegaly reisistant on first-line SSAs. In 2015 therapy was switched to pasireotide LAR 60 mg every 28 days. After two years, the IGF-I level touched the lower age range and therapy was downscaled to pasireotide LAR 40 mg, and in 2020 to 20 mg. In 2021 and 2022, the IGF-I level remained within the normal age range.
Case 2
A 40-year-old female affected by acromegaly resistant on first line SSAs and pegvisomant, who underwent on 3 different neurosurgeries. In 2011 he was enrolled in a Phase III clinical trial (PAOLA study) and assigned to receive pasireotide LAR (60 mg every 28 days). Due to IGF-I overcontrol and radiological stability, in 2016 therapy was downscaled to pasireotide LAR 40 mg and in 2019 further downscaled to pasireotide LAR 20 mg. During the treatment, the patient developed hyperglycemia treated with metformin 500 mg 3 times daily.
Case 3
A 37-year-old male affected by acromegaly resistant on first line SSAs. In 2011 the patient was enrolled in the PAOLA study assigned to receive pasireotide LAR (60 mg every 28 days). In 2018, therapy was downscaled to pasireotide LAR 40 mg for IGF-I overcontrol and in 2022 to pasireotide 20 mg. He developed hyperglycemia, HbA1c values stayed under 6.5% (48 nmol/l) for 7 years.
Discussion
Initiating therapy with a high dose of pasireotide (60 mg) could allow a greater proportion of patients to achieve acromegaly control, particularly in selected cases of clinically aggressive acromegaly that may respond well to pasireotide (characterized by high IGF-I values at diagnosis, invasion of the cavernous sinuses, partial resistance to first-line SSAs and positive expression of SSTR5). Another benefit of this treatment could be the long-term control of IGF-I levels and its oversuppression that continues even when the dose of pasireotide LAR is reduced. The major risk seems to be hyperglicemia. Nevertheless, GH and IGF-I uncontrolled levels are major players in the glucose metabolism. The main limitation of our observation is the very small sample size of our series, to confirm our observations clinical studies are required.
Conclusion
This de-escalation pasireotide treatment could allow to both achieving control of acromegaly and acceptable metabolic tolerance in selected cases of aggressive acromegaly potentially responsive to pasireotide.

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Somatotrpic adenomas: Radiological features at diagnosis in a Tunisian cohort

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Background and aim

Acromegaly is mostly due to a somatotropic adenoma. Regarding its insidious nature, this adenoma is often revealed at an invasive stage. This study aims to describe the radiological specificities of somatotropic adenomas at the time of diagnosis

Patients and methods

We conducted a retrospective study at the Endocrinology department of Hedi Chaker University Hospital, Sfax, Tunisia. We involved 29 patients diagnosed with acromegaly, whose clinical, biochemical, and imaging peculiarities were collected from medical charts.

Results

The mean age at diagnosis was 45.8 ± 12.4 years with a male predominance (51.7%). The majority of patients (60%) presented with symptoms evolving 5 years before the diagnosis. The reasons for consultation were dominated by a pituitary tumor syndrome (30%) or acrofacial dysmorphia (16.6%). A hypothalamic–pituitary MRI was performed in all patients. Somatotropic macroadenomas were predominant, noted in 82.8%. The frequency of microadenomas did not exceed 17.2%. The mean tumor size was 23 ± 10.5 mm. The majority of adenomas (44.8%) were between 10 and 20 mm. Two patients had a giant adenoma (46 mm and 50 mm). A T1 hypo-signal or iso-signal was observed in 47.1% and 52.9% of patients, respectively. On T2-weighted sequences, the adenoma appeared as iso-signal in 44.4%, more rarely as hypo- (27.8%) or hyper-signal (27.8%). Pituitary apoplexy was found in 2 cases. The adenoma was invasive in 48.3%. This invasion was at the expense of the cavernous sinus (20.7%), the supra-sellar cisterns (31%) or the sphenoidal sinus (6.9%).

Discussion

Somatotropic adenomas are classically invasive macroadenomas. Their spontaneous signal is variable but a heterogeneous appearance is frequent, particularly clear in T2. Some studies suggest that a hypointense T2 appearance correlates with high secretory activity (densely granulated cells) and is predictive of a better biological response to somatostatin analogues.

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EP788

Prolactinoma in men

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Introduction

Prolactinomas in men are rare but are characterised by their giant and invasive nature. They present with signs of hypogonadism and mass effect. The aim of this study is to clarify the clinical, biological, radiological and therapeutic features of Prolactinomas in men.

Patients and methods

Retrospective descriptive study including 27 adult males with a prolactin pituitary adenoma hospitalized in the endocrinology department of the Hedi Chaker Sfax university hospital over the period from 1998 to 2020.

Results

The average age of diagnosis was 38.6 years with two peaks of incidence: between 20 and 39 years (59.52%) and between 40 and 59 years (25.9%). The most frequent revealing symptom was mass effect (48.1%) Dcreased libido and erectile dysfunction were found in 85.1% and 81.4% of cases respectively. Gynecomastia was found in 8 patients and galactorrhea in only 2 patients. Prolactin levels above 250 ng/ml were present in 24 patients, 7 of whom had prolactin levels above 10 000. The prevalence of pituitary insufficiency was 85.1%. Gonadotropic deficiency was the most frequent (85.1%, $n=23$) followed by corticotropic and thyroid deficiency (37% and 25.92% respectively). The mean tumour size was 46 mm [9–90 mm]. Giant prolactinomas and macroprolactinomas were the most frequent (48.1% and 40.7% respectively). Only 3 patients had a microprolactinoma. Suprasellar extension was found in 85.2% of cases. Invasion of the cavernous sinus was found in 48.1% of cases and invasion of the sphenoidal sinus in 40.7% of cases. A cystic component was found in giant prolactinomas (30.7%, $n=4$).Radiological apoplexy was found in 29.5% of cases. The first-line treatment was medical in almost all patients. Surgical treatment was performed in 5 patients in the case of resistance to medical treatment in 4 patients and as first-line treatment in the case of chiasmatic compression with visual prognosis in one patient. Complete disappearance of the adenoma was observed in only 5 patients and 63.1% of prolactinomas were resistant to treatment.

Conclusion;

Compared to other types of adenoma. Treatment resistance defined as persistence of the adenoma and/or hyperprolactinemia is common in macroadenoma and invasive tumours. Other factors are very young age, male gender, cystic, haemorrhagic and/or necrotic components on initial imaging. This leaves room for new therapeutic alternatives such as pasireotide and temozolomide.

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EP789

Diagnostic approach and treatment options for a geriatric patient with panhypopituitarism due to pituitary apoplexy

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Pituitary apoplexy (PA) is a rare clinical syndrome related to abrupt hemorrhage and/or infarction of the pituitary gland, usually occurring in patients with preexisting pituitary disease. It is an endocrine emergency requiring rapid diagnosis and appropriate management. Pituitary apoplexy may lead to multiple pituitary hormone deficiencies. Without proper diagnosis and management, these can lead to the occurrence of irreversible complications, most significantly adrenal crisis due to secondary adrenal failure. Secondary adrenal insufficiency is the most common subtype of adrenal insufficiency caused by certain medications and pituitary conditions (pituitary masses, inflammation, hemorrhage or infiltration) and etc. We present a case of 77 y/o male patient who presented in our clinic in June of 2022 with the complaints of fatigue, weakness, voice changes, lethargy and weight loss. His medical history revealed a presence of pituitary macroadenoma diagnosed in 2009, without proper functional status assessment. His medications included levothyroxine 37.5 μg since 03.2022. Patient was hospitalized twice in 2021 due to low blood pressure, nausea, vomiting and syncope but no definitive diagnosis was made. Laboratory work-up confirmed secondary adrenal insufficiency, secondary hypothyroidism and secondary hypogonadism. Patient was referred to radiologist, upon MRI imaging diagnosis of Supra/endosellar neoplasia, with pituitary apoplexy and panhypopituitarism were made. Treatment with hydrocortisone was initiated, levothyroxine was discontinued temporarily and later restarted to avoid adrenal crisis. Patient's clinical condition was significantly improved, he was referred to endocrine surgeon for further assessment. Decision was made to follow-up patient and continue medical treatment. Considering patient's medical history, current clinical status and age, multidisciplinary team approach is recommended to tailor treatment options for individual cases.

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EP790

Werner syndrome and endocrine involvement: A case report

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Introduction

Werner syndrome is a rare genetic disease affecting the WRN gene, of autosomal recessive inheritance.

Case-presentation

We report the case of a 34-year-old patient who presented with erectile dysfunction and asthenia. His brother underwent surgery for meningioma. He was also diagnosed with hypogonadism, suffered from bilateral cataract and diabetes, and died following acute Leukemia at the age of 35 years. Our patient is from a second-degree consanguineous marriage, he has a low intelligence quotient, a bilateral cataract for which he underwent surgery, a growth retardation secondary to a GH deficiency, peripheral hypothyroidism, and diabetes treated with metformin. On examination, he had a hoarse voice, short stature, facial dysmorphia with triangular bird's head face and spread ears, flat feet, and canities. He had hypopigmented areas on the limbs with scleroderma of the skin without melanoderma. Both testicles were in place with a pubertal stage estimated at G3P3 according to Tanner scale. He did not have gynecomastia or micropenis. Hairiness was rare. On biology, he had an HBA1C at 7.2%, hypertriglyceridemia at 6.47 mmol/l, TSH at 2.7 mUI/l, low baseline cortisol level at 32 ng/ml, ACTH

at 50 pg/ml, FSH at 1.3 mUI/l, LH at 5.3 mUI/l, Testosteronemia was low at 0.7 ng/ml and Prolactinemia at 150 µUI/l. The hypothalamic–pituitary MRI was normal. A genetic study revealed a mutation of the WRN gene confirming Werner syndrome. The patient was treated by substitution therapy with Hydrocotrtisone and Testosterone Enanthate along with with dietary rules and Fenofibrate. During follow-up, the patient was diagnosed with a locally advanced nasopharyngeal carcinoma. The patient died as a result of complications related to radiotherapy.
Discussion
Werner syndrome usually begins in adolescence with a peak at age 30. It is responsible for premature aging and affects almost all functions, especially endocrine ones. The latter is manifested essentially by hypothyroidism, hypopituitarism, and hypogonadism. Hypothyroidism is generally peripheral due to atrophy of the thyroid gland, but central hypothyroidism remains possible. Hypogonadism is essentially a hypergonadotropic hypogonadism due to premature atrophy of the reproductive organs. Hypogonadotropic hypogonadism may be found more rarely, probably in relation with hypopituitarism. Diabetes observed in this syndrome is due to insulin resistance and decreased insulin secretion. The prognosis is linked to the occurrence of early and aggressive cancers.

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EP791

Pituitary formation according to the results of magnetic resonance imaging studies

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Objective
The introduction of imaging technologies into routine clinical practice has increased the pituitary incidentalomas cases detection by magnetic resonance imaging (MRI) of the brain. Identification of pituitary formations requires additional hormonal examination and dynamic MRI pituitary examination for differential diagnosis and treatment strategy for patients. An important clinical problem is to determine the malignancy, predictors of potential growth and hormonal activity of pituitary incidentalomas from the results of MRI studies.
Materials and methods
A preview of retrospective study patients with pituitary incidentalomas detected by pituitary MRI examination at Republican clinical hospital of medical rehabilitation in 2021–2022 years is presented. All patients underwent pituitary MRI without gadolinium using at the beginning. In doubtful cases, repeated MRI was performed with gadolinium. Sagittal and coronal scans were examined. A pituitary macroadenoma was diagnosed with a one size of 10 mm or more. Laboratory, clinical and MRI data were analyzed using a neural network. Our neural network architecture consists of two consecutive parts. Detection model presented as a one-stage object detection neural network (Retina Net) to produce bounding boxes of the pituitary. Diagnosis model: ResNet-34 used to predict probabilities of pituitary macro/microadenoma using output of previous neural network (segmented slices). Derived probabilities was combined with hormonal tests via Gradient Boosting on Decision Trees algorithm.
Results
We studied 310 patients with pituitary incidentalomas, average age 40.9 ± 15.91 years. A pituitary macroadenoma was diagnosed in 24 (7.7%) patients, average age 50.8 ± 14.09 years, male:female rate was 1:2 (male – 8 (33.3%), female – 16 (66.7%)). 286 patients with pituitary incidentalomas less 10 mm, average age 36.2 ± 13.55 years. Pituitary macroadenoma was significantly more frequently diagnosed in older patients compared to younger ones ($P < 0.05$). Pituitary incidentalomas less than 10 mm were more frequently diagnosed in young patients ($P < 0.05$).
Conclusion
The results of the study indicate an increased prevalence of pituitary macroadenomas in women and associated with an increase in age. It is necessary to clarify the plan for long-term monitoring of incidentalomas in young people for timely detection of growth.

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EP792

Pituitary pathology and pregnancy

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Introduction
Pregnancy in patients with pituitary pathology is a rare and delicate situation. However, risks for the mother and the foetus as well as the consequences of pregnancy on the history of pituitary adenoma require close monitoring.
Goals
Illustrate through 5 observations the evolution of pituitary pathology during pregnancy.
Observations
1st patient: 41-year-old followed for somatotropic pituitary macro adenoma for which she was operated on with treatment failure. Pregnancy occurred 2 years post-operatively, with a preconception IGF1 level twice normal; MRI performed at 10 WA showed regression in the size of the adenoma, without visual complications. The delivery was scheduled at 37 WA by cesarean section without complications. The patient breastfed for 20 days and then stopped when the tumor syndrome accentuated.
2nd patient: 29 years old, followed for somatotropic pituitary macro adenoma operated on twice by transsphenoidal approach with treatment failure, then received medical treatment. The pregnancy was uneventful with unassisted home birth without complications. The patient breastfed for 20 months, currently, the child is 30 months old with good psychomotor development.
3rd patient: 37 years old who presented during the second trimester of pregnancy with a Cushing syndrome on pituitary macroadenoma with visual complications. Treatment consisted of complete transsphenoidal resection at 13 weeks. The evolution was marked by the occurrence of a spontaneous abortion at 20 SA.
4th patient: 35 years old followed for Cushing disease operated on with recurrence. The indication for a surgical revision was posed after medical preparation which was stopped in front of the discovery of pregnancy. The revision surgery was planned after delivery. The pregnancy was carried to term without complications. The delivery was vaginal without complications. The patient breastfed for 12 months.
5th patient: 36 years old followed for Cushing disease for 2 years on pituitary microadenoma operated and complicated by corticotropic insufficiency in remission. The pregnancy occurred 3 months later with good clinical evolution. The delivery was vaginal without complications, and the patient did not breastfeed.
Conclusion
Pregnancy is rare in patients with pituitary adenoma. On the other hand, its occurrence most often requires multidisciplinary and close care to prevent maternal and fetal consequences.

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EP793

Metabolic complications of acromegaly: About 62 cases

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Introduction
Metabolic disorders caused by acromegaly are responsible for three times the morbidity of the general population
Study objectives
To analyze the different metabolic complications in acromegalic patients.
Materiel and methods
This is a retrospective study of 62 cases of acromegaly followed at the Department of Endocrinology and Metabolic Diseases CHU IBN ROCHD from January 2005 to December 2022. The data analysis was done with the Excel software in its 2021 version.
Results
The mean age was 54 years (17–88), Sex Ratio: F/H of: 2.6, the age of the disease at diagnosis averaged 10 years, the mean IFG1 level was 721.53 ng/ml. The average BMI level was 29 kg/m^2. The clinical examination found overweight in 15 patients or 24.19%, and obesity in 28 patients or 45.16%. The metabolic balance objectified carbohydrate metabolism disorders: prediabetes in 14 patients or 22.5% and diabetes in 27% patients or 43.5%. Dyslipidemia was objectified in 35 patients or 56.45% with a mean cholesterol level of 2 g/l, mean triglyceride of 1.7 g/l, mean HDL of 0.43 g/l and mean LDL level of 1.2 g/l. Hyperuricemia in 5 patients or 8% with an average uric acid level of 45 mg/l. All patients with carbohydrate metabolism disorders were put on hygiene-dietary measures, and in 74% on oral antidiabetics (ADO), and 21% on insulin therapy + ADO. Patients with dyslipidemia, were put in addition to hygiene-dietary measures adapted to statins in 65.2%. A marked improvement in the control balances has been achieved.
Conclusion
The systematic screening of metabolic complications in acromegalic patients and their early and adequate management is of major interest in order to prevent morbidity and mortality which results mainly that related to vascular accidents

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EP794

MAFLD prevalence in a cohort of patients with Cushing's disease

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Objectives
To describe the prevalence of liver steatosis in a cohort of patients with Cushing's disease.
Methods
Cross-sectional descriptive study. We included 59 patients with Cushing's disease from our cohort of patients who underwent a Fibroscan to analyze the degree of hepatic steatosis (CAP measured in dB/m) and liver fibrosis (fibrosis measured in kPa). Biochemical algorithms of liver steatosis and fibrosis were assessed.
Results
7 (11.9%) men and 52 (88.1%) women. Median age 52 [43–61] years with 9.3 [3.7–18] years of follow-up. 40 (67.8%) cured and 19 (32.2%) non-cured. Median years of hypercortisolism was 2.13 [0.76–5.17] years. 26 (44.1%) showed any pituitary defficiency, 18 (30.5%) ACTH defficiency, 7 (11.9%) sex hormones defficiency and 16 (27.6%) thyroid. Metabolic morbidities were, obesity in 29 (48.3%) patients, type 2 DM 16 (27.6%), HBP 30 (50.8%), dyslipemia 29 (49.2%) and **4 (6.9%) chronic renal disease**. As mayor cardiovascular disease (3, 5.1%) suffered hearth disease and 2 (3.4%) an stroke. Four (6.8%) had chronic renal disease. 55.9% patients showed any degree of MAFLD with a median CAP of 265 [212–288] db/m. Two (3.4%) patients were diagnosed with liver fibrosis (kPa compatible with F3-F4). MAFLD was associated with obesity, time of hypercortisolism, curation, type 2 DM and hypertrigliceridemia.
Conclusions
The prevalence of MAFLD in patients with Cushing's disease is high and higher than described in previous studies. Hepatic steatosis is associated with variables related with the metabolic syndrome and the curation of Cushing' s disease. It is postulated that despite metabolic control, there is an increased risk of hepatic steatosis in uncured patients. A low percentage of liver fibrosis has been observed compared to the degree of fibrosis.

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EP795

Coexistence of acromegaly and autoimmune disorders: Between hazard and causality – a case series

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Introduction
Acromegaly is a rare, chronic endocrinopathy, that results from persistent hypersecretion of growth hormone (GH) and consequently of insulin-like growth factor 1 (IGF1). It is well known that GH excess has multisystemic effects throughout the body, but its interaction with the immune system has only been suggested in the last few decades. This prompted us to explore the frequency of autoimmune disorders in a retrospective acromegaly cohort.
Case description
We present 7 cases of acromegaly occurring in association with autoimmune diseases, other than autoimmune thyroiditis, that have been evaluated in our clinic between 2015 and 2022. Two patients were diagnosed with myasthenia gravis (one of them with concurrent Graves disease), two with vitiligo, one patient had antineutrophil cytoplasmic autoantibodies (ANCA) associated vasculitis, another patient displayed a case of severe rheumatoid arthritis, and one had generalized psoriasis. The mean age at diagnosis was 47.4 years for acromegaly and 47 for autoimmune diseases, with a 6:1 female to male ratio. The most common presenting symptom for acromegaly was headache (57%), whilst autoimmune disease manifestations varied from fatigue and unilateral eyelid twitching to thrombotic events and acute kidney failure. Six patients had pituitary macroadenomas and only one had a microadenoma with a mean IGF1 at diagnosis of 2.9× upper limit of normal. The diagnosis of acromegaly preceded the autoimmune disease confirmation in only three cases, with an estimated duration of 40.3 months; was concomitant with the diagnosis of one myasthenia gravis case and was established during the evolution of vitiligo and rheumatoid arthritis in the other three patients. Six patients (86%) underwent surgery (one of them had two interventions), 4 of which (57%) required additional therapy for biochemical control consisting of somatostatin analogues (SA, $n=3$) or combination therapy with SA and cabergoline ($n=1$). One patient was treatment-naïve. Complete biochemical control was achieved in 5 patients (71%) and 2 out of 3 patients had controlled acromegaly at the time of the autoimmune disease's diagnosis. Complications of acromegaly or autoimmune diseases were identified in 86% of cases.
Conclusion
Despite the increasing evidence of the immunomodulatory actions of the GH/IGF1 axis, the reports on autoimmune diseases in acromegaly patients are sparse. Considering the increasing prevalence of this disorders and the debilitating complications of both acromegaly and autoimmune afflictions, the interaction between GH excess and a dysregulated immune system should be further analysed.

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EP796

Octreotide and pasireotide LAR in non-functioning pituitary neuro-endocrine tumours treatment

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Somatostatin analogues (SSA) are first/second line treatment in the management of acromegaly and Cushing disease (CD), however, recent data suggest that they can be effective in the management of non-functioning pituitary neuroendocrine tumour (PitNET). We present one clinically silent gonadotroph PitNET treated with octreotide and two silent corticotroph PitNETs treated with pasireotide.
Case 1
A 50-year-old female presented with frontal headache and visual field deficits. In magnetic resonance imaging (MRI) a pituitary mass 30×34×34 mm with suprasellar expansion, compressing third ventricle and optic chiasm, invading sphenoid and cavernous sinus was described. She underwent transsphenoidal surgery (TSS), however, due to residual mass 34×28×37 mm a second TSS was performed. In histopathology gonadotroph PitNET; LH-, FSH +, SF1++, Ki-67<1%, SSTR2A++ was described. In control MRI 32×32×22 mm mass was visualised, patient has been continuously suffering from severe headaches. After multidisciplinary tumour board Octreotide LAR 20 mg/monthly was introduced. After 6 months of treatment, milder headaches and stable pituitary mass were noted.
Case 2
A 33-year-old male was admitted to Emergency Department due to severe headaches (8–9/10 using numbering rating score (NRS)) and vomiting. Sellar tumour (39×33×55 mm) and cerebral edema were found. External ventricular drainage and TSS were performed. Histopathology results showed silent adenoma subtype 1 (densely granulated), Ki67<1%. Three months later, MRI showed progression of PitNET (40×39×30 mm). Subsequently, patient underwent two emergency TSS and stereotactic fractionated radiotherapy. Treatment with temozolomide, pasireotide, cabergoline, radiotherapy was introduced. After 18 months of combined therapy stable disease was observed. Implementation of pasireotide resulted in spectacular decrease of headaches (initially 9–10 to none /10 using NRS).
Case 3
A 31-year-old male presented in our clinic due to headaches and bitemporal hemianopsia. In MRI PitNET was found (22×19×23 mm) and active CD was diagnosed. TSS was performed in 2013. Histopathology results showed corticotroph PitNET with Crook cells. Postoperatively, PitNET progression (17×26×13 mm) was observed with no overt CD. In 2022, due to worsening of headaches and vision loss, second TSS was performed. Histopathologists described corticotroph tumor with Crook cells with ATRX mutation of uncertain significance. Pasireotide implementation is planned. Pharmacotherapy with SSA in the cases of non-functioning PitNETs allows the stabilisation of the disease, decrease the headaches and can be considered as an alternative for the next neurosurgeries, however, further multicentre studies should be carried out.

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EP797

Pituitary stalk interruption syndrome: A rare and severe cause of hypoglycemia in the newborn

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Introduction
Pituitary Stalk Interruption syndrome (PSIS) is a congenital anomaly of the pituitary gland responsible for isolated or combined anteropituitary insufficiency. We report a case of Pituitary Stalk Interruption Syndrome (PSI) diagnosed in a newborn with profound hypoglycemia.
Case report
We report the case of a newborn with hypotonia, neonatal jaundice associated to a micropenis and a bilateral cryptorchidia. Because of severe hypoglycemia at 1.80 mmol/l (0.33 g/l), persistent despite infusions of glucose serum and glucagon, a hormonal assessment was requested at 48 h of life revealing corticotropic, thyroid and somatotropic insufficiency in favor of a congenital pituitary deficiency. A hypothalamic–pituitary MRI revealed a complete interruption of the pituitary stalk, an ectopic post pituitary associated with hypoplasia of the corpus callosum without other cerebral anomalies. Immediate hormone replacement therapy with hydrocortisone and Lthyroxine resulted in clinical improvement. Growth hormone treatment was also delivered for metabolic and neurodevelopmental purposes to limit the risk of further hypoglycemic episodes. The gonadotropic axis was explored at 6 weeks of age and revealed congenital hypogonadotropic hypogonadism, which led to the initiation of androgen therapy.
Discussion-conclusion
Complete or incomplete pituitary stalk syndrome is a rare syndrome defined by morphological abnormalities on MRI: small or interrupted pituitary stalk, hypoplastic anteroposterior pituitary and ectopic or absent posterior pituitary. The precise pathophysiology of this syndrome is discussed but the theory of congenital malformation with associated midline malformations is retained. Despite the fact that SITP is a rare disorder, it should be considered as a differential diagnosis in the newborn with severe hypoglycemia.

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EP798

Pituicytoma in 64 years old man

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Introduction
Pituicytoma is a rare, primary benign, tumor of the sellar and suprasellar regions which is arising from pituicytes of the neurohypophysis and infundibulum and mainly affects middle age adults. We present here such a case
Presentation
A 64-years-old man was referred to our clinic. For further investigation of a sellar lesion with suprasellar extension. The patient underwent investigations due to visual disturbances which he noticed initially 6 months ago and gradually became worse. On opthalmological examination he found to have bitemporal hemianopsia and magnetic resonance imaging (MRI) of the brain and the pituitary revealed a well-circumscribed lesion about $2\times2\times1.8$ cm in size in sellar region with suprasellar extension, compressing the optic chiasm. The lesion was isointense on T1- and T2-weighted images, with heterogeneous enhancement following intravenous administration of Gd-DTPA. Clinical examination and laboratory testing did not reveal any hormonal deficiencies. Trans-sphenoidal surgery was carried out for optic nerve decompression, but full removal of the lesion was not possible due to bleeding during the operation. Histopathological examination revealed tumor cells spindle shaped, with unclear boundary and abundant cytoplasm. The tumor displayed diffuse immunoreastivity for TTF-1, S-100, focally GFAP and vimentin. These findings are typical features of pituicytoma. Following the surgery, the patient developed transient diabetes insipidus and his bitemporal hemianopsia was improved.
Conclusions
Pituicytoma is a rare tumor with less than 200 patients to be reported in the literature. It can be detected either as an incidental finding due to increasing imaging or due to symptomatology related to location and the tumor size. Clinical symptoms can include visual disturbances, headache and hypopituitarism. The diagnosis is based on histopathological examination which reveals the typical morphological and immunohistochemical features of pituicytoma.

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EP799

Craniopharyngiomas in adult patients: Retrospective, multicentric study in Buenos Aires, Argentina

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Craniopharyngiomas are rare lesions derived from cell remnants of Rathke's pouch, usually localized in the sellar and suprasellar areas.
Objectives
To analyze clinical, endocrine and histological features in a group of patients from Buenos Aires city. To assess efficacy, number of surgeries and complications after surgery or other treatments.
Material and methods
Multicentric, retrospective, transversal study. Adult patients with craniopharyngiomas were included. We assessed clinical, biochemical, MRI features, at diagnosis and after treatments, the follow-up and recurrence of tumors.
Results
Ninety-seven patients, 49 women. Mean age at diagnosis: 41.4 ± 16.04. Symptoms at diagnosis: visual field defects (VFD): 47.4%, headache: 14%, both symptoms: 14%, in this group with mass effect, the VFD reached 61.8%. Other symptoms at diagnosis: incidental findings: 8,2%, diabetes insipidus (DI) 5.2%, and others 11.2% (n:10): 4 hypopituitarism, 2 oligomenorrhea, 2 neurocognitive deficit, 1 behavior disorder, 1 intracranial hypertension. Supraselar extension was present in 88.7%. Endocrine tests showed: hyperprolactinemia 27.8% (Prolactin levels: 61.6 ng/ml (21-156). DI and panhypopituitarism (PHP) were present in 30.5 and 26% respectively; VFD 78.5%: hemianopsia (60.9%): 50/82, quadrantopsia 19% and blindness 10.5% (9/85). Basal BMI was 28.6 ± 7.6. Surgical treatment (95/98): transcranial approach was performed in 71.1%, transsphenoidal approach was used in 25.8%; gross total resection was reached in 46.4%, subtotal 37.1% and partial resection 14.4%. Adamantinomatous type was found in 58.8%, papillary type in 13.4%. In the post-surgical assessment: 71.1% developed (PHP) (p .002) and DI 64.9% (p.002). VFD were 45.4% (40/88): hemianopsia 36.4%, quadrantopsia 9.5% and unilateral or bilateral amaurosis 9% (P 0.002 vs pre surgery). Tumor remnants were observed in 46.8% and recurrence rate was 19.6%. A second surgery was performed in 42.3%. Radiotherapy was indicated in 9.6%. Median time of follow-up was 57 months (4-427). Nine patients died, 4 related to the craniopharyngioma.
Conclusions
In this cohort of adult patients with craniopharyngiomas, VFD was the main symptom. Transcranial approach was the predominant surgery; Adamantinomatous type was the most frequent. In the post-surgical assessment, there was significant improvement in the visual field, but a significant increase in the BMI of patients and in the number of subjects with PHP. A second surgery was performed in 42.3% and 9.6% was treated with radiotherapy. These patients with long-term morbidities need life-long follow-up by a multidisciplinary team

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EP800

Metastatic insulinoma in MEN1 patient

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We present a case report of a 56-year-old woman with MEN1 syndrome diagnosed at the age of 28 years. It was completely expressed by the set – insulinoma, prolactinoma and primary hyperparathyroidism. She underwent resection of 2/3 of the pancreas for symptomatic hypoglycaemia in the age of 28 years (1991). After two resections of parathyroid glands hypocalcaemia replacement was necessary. Prolactinoma was transiently treated with dopamine agonists. In the age of 45 years hypoglycaemia symptoms reappeared and a 30 mm recurrence of neuroendocrine tumour in the pancreatic head was detected. After its surgical enucleation (complicated with pancreatic fistula) hypoglycaemia symptoms improved, but did not completely disappeared. On abdominal ultrasound examination, small multiple hyperechogenic foci in the steatotic liver were observed. From the age of 53, the size of the largest lesion in segment VI progressed to 25 mm, then after one year to 30 mm. Clinical complaints included symptoms of hypoglycaemia – weakness, sweating, trembling hands, resolution of symptoms after eating. Whole-body scintigraphy after administration of ^{111}In-pentetreotide (Octreoscan) did not show expression of somatostatin receptors in the liver foci. A biopsy of the lesion in the right lobe of the liver followed in November 2022. The liver histology confirmed metastases of pancreatic insulinoma – NET G1 with the somatostatin receptors 5 (SSTRs-5) positivity (about 90% of cells, 2-3+). Recently, microwave ablation of the largest liver lesion was performed. The clinical manifestations were relieved and glycaemia normalized shortly after microwave liver ablation. In our case, recurrence of liver metastases of malignant insulinoma in the liver occurred 28 years after the diagnosis of MEN1 syndrome. The tumour strongly expressed SSTR-5 on liver metastases, but no SSTR-2 was revealed, which is rare and explains Octreoscan negativity. Thus, further pasireotide therapy was indicated with the aim of antisecretory and antiproliferative effect on neuroendocrine tumour.

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EP801

An Open-Label Extension Study to Evaluate the Safety of Long-term Use of Relacorilant in Patients With Endogenous Cushing Syndrome

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Cushing syndrome (CS) is a chronic and debilitating condition with high morbidity and mortality. Development of novel, safe, and effective pharmacologic therapies with improved risk-benefit profiles would enrich treatment options for patients. Relacorilant is a selective glucocorticoid receptor (GR) modulator that competitively antagonizes cortisol activity and, unlike the FDA-approved GR antagonist mifepristone, does not bind to the progesterone receptor. In a phase 2 study in patients with endogenous CS (NCT02804750), relacorilant treatment was associated with clinically meaningful improvements in hypertension and hyperglycemia without undesirable antiprogesterone effects or drug-induced hypokalemia (Pivonello *et al. Front Endocrinol.* 2021;12:662865). GRACE (NCT03697109) and GRADIENT (NCT04308590) are ongoing phase 3 trials of relacorilant in patients with endogenous CS and concurrent hypertension and/or hyperglycemia. This abstract presents the study design of the phase 2/3, single-arm, open-label extension study (NCT03604198; EudraCT 2018-001616-30) evaluating the long-term safety and therapeutic effect of prolonged GR modulation with relacorilant. Study participants must have successfully completed one of the parent studies of relacorilant (NCT02804750, NCT03697109, NCT04308590) and, in the investigator's opinion, may benefit from further treatment. Biochemical entry criteria are consistent with the parent studies. For participants who completed relacorilant treatment >12 weeks before entering the extension study, reconfirmation of hypercortisolism is required. Participants receive daily relacorilant at the last dose received in their parent study unless dose modification is indicated by the investigator's clinical judgment. For participants entering from a placebo-controlled study or if the last dose of relacorilant was >4 weeks before enrollment, the starting dose is 100 mg oral capsule once daily, titrated up to the maximum tolerated dose not to exceed 400 mg. Treatment continues until relacorilant is commercially or otherwise available or until the study is stopped by the sponsor.

Primary endpoints are the incidence of treatment-emergent adverse events and changes from baseline in:

- Clinical laboratory tests
- Physical examinations and vital signs
- 12-lead electrocardiograms
- Pituitary tumor size based on magnetic resonance imaging for participants with Cushing disease

Exploratory endpoints assess the long-term benefit of relacorilant in the treatment of signs and symptoms of endogenous CS, including changes from baseline in the parent study in hemoglobin A1C, impaired glucose tolerance, and blood pressure. Additional exploratory endpoints include changes from baseline in body weight and composition, quality of life, bone remodeling, and other metabolic covariates of interest. This study is currently open for enrollment at centers in Europe, Israel, and North America.

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EP802

Diagnostic and therapeutic challenges in cyclic Cushing's syndrome: A systematic literature review

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Background

Cyclic Cushing's syndrome (cCS) is a sub-entity of Cushing's syndrome (CS) associated with diagnostic and therapeutic challenges. It describes a condition, in which phases of clear-cut biochemical hypercortisolism are followed by spontaneous troughs of normal or subnormal cortisol secretion. We conducted the first systematic literature review to identify common features of cCS.

Methods

We searched MEDLINE (via PubMed) for eligible single case reports and case series from inception to October 10th, 2022, using two independent search terms. We compared outcomes to patients with noncyclic CS derived from the literature and to a longitudinally enrolled cohort from LMU hospital Munich as a reference standard.

Findings

In total, 212 cases with cCS were included for further analysis. Pituitary tumor origin accounted for 143 (67%), ectopic for 36 (17%), and adrenal for 23 (11%) cases. 4 (2%) cases were of occult origin, and 6 (3%) cases were unclassified. Clinical signs and symptoms were comparable to non-cyclic CS. In ACTHdependent forms, inferior petrosal sinus sampling had a positive and negative predictive value of 100% when performed during hypercortisolism vs 76% and 29% when performed irrespective of cortisolemic status. Overall, twelve (6%) patients underwent unnecessary surgery due to misdiagnoses. Remission rates were significantly lower and time to remission significantly longer when compared to the population with non-cyclic CS ($P < 0.001$).

Interpretation

We identified a heterogeneous population of patients with cCS with various tumor etiologies. Unpredictable cycle duration and frequency may cause diagnostic challenges resulting in misdiagnoses and missed diagnoses.

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EP803

Rheumatologic complications of acromegaly

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Introduction
The osteoarticular complications of acromegaly are among most disabling impacts, and can be explained by two mechanisms, chronic exposure to high levels of GH and IGF1 leading to increased bone turnover, hypertrophy and osteocartilaginous degeneration, as well as the gonadal insufficiency observed during acromegaly may aggravate the situation. The objective of this study is to describe the rheumatological manifestations of acromegaly.
Materials and methods
This is a descriptive study of 25 patients followed up in the endocrinology, diabetology and nutrition department of the Mohammed VI University Hospital center in Oujda. All patients had a complete clinical examination, a phosphocalcic assessment and a bone densitometry.
Results
The mean age was 49.1 ± 14.4 years (24-71) with a sex ratio (M/F) of 1.08. The mean age of the diagnostic disease was 71 years and the mean IGF-1 level was 706.5 ± 257.8 ng/mL. Peripheral articulation manifestations included diffuse arthralgias and acromegalic arthropathy, which were present in 69.6% and 28.6% of the cases respectively. Axial affection was dominated by spinal pain, which was present in 30.4% of cases, accompanied by scoliosis and cervical hyperlordosis in 16% and 48% respectively, and vertebral fractures were found in 13% of cases. Neuromuscular manifestations with carpal tunnel syndrome were reported in only one patient. The evaluation of the phosphocalcic assessment finds vitamin D deficiency in 83% of cases. Bone densitometry showed osteoporosis in 16.7%, osteopenia in 44.4% of patients.
Discussion - Conclusion
The rheumatological complications of acromegaly are the principal causes of functional incapacity, hence the interest in seeking them out early in order to reduce their impact on the functional prognosis. Our results confirm the frequency of these manifestations detected at the time of diagnosis or follow-up of acromegaly, underlining the need for a multidisciplinary approach in order to improve the quality of life of patients.

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EP804

Correlation Betwen Obesity in Patients with A Diagnosis of Non-Functioning Adenomas and Prolactinomas

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Background
Obesity is a chronic and complex health problem. Although it is a preventable health risk factor, iís prevalence has grown rapidly in recent years. There are studies that demonstrate the relationship between hyperprolactinemia and obesity. However, it is not well explained and the results are contradictory. The objective of this study was to evaluate the relationship between increased prolactin and Body Mass Index (BMI) in patients with pituitary macroadenomas.
Methods
A retrospective case-control study was carried out by extracting information from medical records of patients with non-functioning macroadenomas and macroprolactinomas, taking into account the difference in prolactin level due to their functionality; excluding other lesions of the sella turcica. The study population was under hormonal supplementation of the affected axis in the case of have it. Descriptive statistics and subsequent odds ratio analysis were performed.
Results
112 patients were included, of which 44 were prolactinomas and 68 non-functioning adenomas, with no significant difference between gender. The current mean age was 44.29 years (SD 15.77), the average BMI 29.59 Kg/m2 (SD 5.11), the mean tumor size was 32.53 mm (10 to 75). Mean prolactin values measured in non-functioning adenomas were 34 ng/mL (2 to 111) and prolactinomas 5800 ng/mL (217 to 47,000). 44.7% of the sample had a BMI greater than 30 kg/m2. In the Odds Ratio analysis we obtained a value of 1.636 (interval 0.774-3.576) indicating that there is no relationship between the amount of prolactin and the risk of developing obesity.
Conclusion
Despite previous evidence demonstrating a relationship between prolactin and obesity risk due to changes in the functionality of adipose tissue, lipid metabolism, insulin resistance and hypothalamic cathepsin and kisspeptin secretion. In this study, relating two populations with similar characteristics in terms of gender, tumor size, and age, we found that the increase in prolactin was not related to having a greater risk of obesity. Taking into account that in our general population 19.93% have obesity (ENSANUT 2018), in our universe 44.7% present this condition. Due to the findings of a higher BMI in the population with the presence of a sellar lesion, we recommend weight approaches in the population group studied, regardless of their functionality.
Keywords
Pituitary adenoma, prolactinoma, hyperprolactinemia, obesity
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EP805

Secondary amenorrhea revealing pituitary sarcoidosis: a case report and review of the literature

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Introduction
Hypothalamic-pituitary involvement during sarcoidosis is rare, less than 1%. Granulomatous infiltration can lead to anteropituitary insufficiency, disconnection hyperprolactinemia and diabetes insipidus. We report a case of hypothalamic-pituitary sarcoidosis with review of the literature.
Observation
Patient aged 39 years, she complains of chronic headaches for 10 months without decrease in visual acuity, secondary amenorrhea for 6 months. The clinical examination reveals a bilateral multiporous induced galactorrhea. The hypothalamo-hypophyseal MRI showed a thickening of the pituitary stem. The hormonal assessment revealed a cortisol level of 3.6 mg/dl at 8 o'clock in the morning, prolactin at 64.6 ng/ml, FSH at 0.7 mIU/ml, LH at 0.6 mIU/ml, estradiol: 5ng/l, TSH us at 2.08 uIU/ml, free thyroxine (T4L) at 12.7 pmol/l, corrected calcemia at 89.49 mg/l, the visual field showed no abnormality. The general work-up revealed a pulmonary localization with a stage II sarcoidosis on the thoracic CT scan and a skin involvement confirmed on biopsy: an aspect of epithelioid and gigantocellular granulomatous hypodermitis without caseous necrosis. The patient was put on corticosteroid therapy and hormone replacement therapy with estrogen-progestin
Discussion
Sarcoidosis is a chronic systemic disease of unknown etiology characterized by the presence of epithelioid granuloma without caseous necrosis. Neurosarcoidosis is found in 5-26% of patients with sarcoidosis. Isolated hypothalamic-pituitary involvement is rare, representing 0.5% of sarcoidosis cases and 1% of sella turcica lesions. The endocrine disorders most frequently encountered in neurosarcoidosis are: diabetes insipidus, hyperprolactinemia and to a lesser degree hypogonadism. However, a review of the literature published by Anthony *et al* classified the endocrine disorders in order of frequency: central hypogonadism in 88.8% of cases, central hypothyroidism in 67.4% of cases, diabetes insipidus in 65.2% of cases, low GH levels in 54% of cases, low ACTH levels in 48.8% of cases, hyperprolactinemia in 48.8% of cases. The most common radiological abnormalities in neurosarcoidosis are multiple white matter involvement (43%) and pathological contrast of the meninges (38%), rarely obstructive hydrocephalus or spinal cord involvement. Imaging may be normal in 12% of cases. The treatment is mainly medical with administration of corticosteroids; in case of poor response to corticosteroids, other therapies may be prescribed such as immonosuppressive drugs and immunomodulators; radiotherapy may also be indicated in some refractory cases.
Conclusion
Hypothalamic-pituitary involvement in sarcoidosis is rare with more frequent complications, the diagnosis is often late. It requires a multidisciplinary management.

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EP806

Analysis of The Modulating Effect of Melatonin on Reproductive Processes and Cognitive Potential Under Conditions of Chronic Inflammation Using The Model of Estrous Cycles of Sexually Mature Female Rats

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Introduction
Reproductive processes are regulated with the participation of the kisspeptinergic neurotransmitter system and the hormonal axis hypothalamus – adenohypophysis – gonads. The action of all regulators of reproductive processes can be disturbed by the development of inflammation and the action of pro-inflammatory cytokines. In this case, cognitive dysfunctions may occur, since sex hormones are involved in the regulation of brain functions. The study analyzed the effect of melatonin on the course of the estrous cycle and cognitive functions of adult female rats under conditions of an experimental model of chronic inflammation (the effect of LPS – lipopolysaccharide *Salmonella typhi*).
Methods
To create chronic inflammation, group A rats received LPS (i.p., 50 μg/kg) daily for 10 days. Group B rats received LPS with melatonin (oral, 0.5 mg/kg) for 10 days. Rats in the control group received sterile water. The phases of the estrous cycle were determined by the ratio of different cell types on stained vaginal smears by light microscopy. The behavior of rats in all experimental groups was tested under the following experimental conditions: open field, elevated plus maze, Barnes' maze, extrapolation escape.
Results
Exposure to LPS in group A led to disruption of the estrous cycle. The duration of diestrus increased by 28% ($P< 0.05$). In vaginal smears, the number of epithelial cells with destruction of organelles significantly decreased, the karyopicnic index decreased by 24% ($P< 0.05$). The action of melatonin reduced the pathological effect of inflammation on the estrous cycle. Group A rats showed a low level of exploratory activity in the open field. In the Barnes maze, group A rats spent more time searching for a safe haven and showed more erroneous responses. In the extrapolation escape test, group A showed an increase in the time to escape from a stressful situation. Rats treated with melatonin maintained higher levels of cognitive ability on various tests.
Conclusions
Melatonin reduces the pathological influence of the used inflammation model on the neuroendocrine mechanisms of regulation of the estrous cycle and cognitive functions. It is likely that the established effects of melatonin may be related to its immunomodulatory and neurotropic properties.

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EP807

Co-occurrence of premature ovarian insufficiency and Rathke Cleft Cyst: case report

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Introduction
Rathke cleft cysts (RCC) are benign cystic lesions of the sellar and suprasellar region, which is believed to arise from the remnants of the Rathke pouch. Symptomatic RCC are rare. Endocrine symptoms are usually caused by compression of the surrounding pituitarygland. It can therefore cause hypopituitarism, but it is rarely associated with primary endocrine dysfunctions. In this case, we report a co-occurrence of premature ovarian insufficiency and RCC.
Case summary
We report the case of a 29-year-old female patient, who first presented with headaches, irregular menses and galactorrhea. Initial investigation showed a hyperprolactinemia with a level of 154 ng/mL without other hormonal abnormalities (TSH:1,27 μUI/ml, fT4: 16,7 pmol/l, cortisol at 428 nmol/l and 603 nmol/l after ACTH stimulation test). Initial hormonal investigation for FSH and LH were at normal levels. Cerebral MRI showed intrasellar cystic low density lesion of 7mm with ring enhancement which evoked a Rathke cleft cyst. She was treated initially with bromocriptine with a well evolution. Interestingly, despite normalization of prolactine levels after two years and disappearance of the galactorrhea, our patient began to have secondary amenorrhea with hot flashes. Hormonal investigation showed hypergonadotropic hypogonadism with high levels of FSH (79,61 mUI/mL) and LH (37,21 mUI/mL). Pelvic ultrasound revealed decrease in both ovaries volume but did not show any other abnormalitites. Genetic testing showed a normal karyotype. The diagnosis of primary ovarian insufficiency was held. The patient received hormone replacement therapy and reported better quality of life.
Conclusion
Rathke cleft cyst occurs mostly in females and may result in a variety of symptoms. Hyperprolactinaemia is the commonest associated endocrine dysfunction, followed by hypopituitarism. This hyperprolactinaemia due to RCC may predispose to autoimmune thyroiditis; however, the association between RCC and primary thyroid disease remains to be clarified.

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EP808

Infectious manifestations during neuro-gastrointestinal mitochondrial encephalopathy: about 2 patients

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Introduction
Mitochondrial neuro-gastro-intestinal encephalopathy (MNGIE) is a rare autosomal recessive disease caused by a mutation in the TYMP gene.
Patients-methods
Retrospective study including 2 cases (brother and sister) followed for MNGIE confirmed by genetic study at the endocrinology department of Sfax.
Results
-> 1st case: 25-year-old man, follow-up for diabetes, dilated cardiomyopathy, renal lithiasis, MNGIE.
He presented :
- A cerebral abscess treated by surgery, without bacteriological documentation at the age of 19,
- Recurrent severe oral candidiasis due to Candida albicans
- Documented parenteral feeding catheter sepsis due to Staphylococcus lugdunensis
- Sequelae of ocular toxoplasmosis

-> 2nd case: 22-year-old woman followed for functional anterior pituitary insufficiency. She presented with recurrent oral candidiasis due to Candida albicans, died of digestive complications
Discussion
The prevalence of infections during MNGIE is 7.9% but no particular association candidiasis and MNGIE For our patients, the acquired immune deficiencies have been eliminated (negative HIV serology and tuberculosis investigation), the dosage of immunoglobulins could not be carried out
Conclusion
The prognosis of MNGIE is severe and linked to the severity of the digestive attack with the occurrence of infections and the use of permanent parenteral nutrition.

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EP809

The importance of Prompt Treatment of Ectopic Cushing Syndrome

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Introduction
Ectopic ACTH production accounts for up to 20 percent of ACTH-dependent Cushing syndrome (CS). Small cell carcinoma and carcinoid of the lung represents half of its cases. These patients lack some of the more obvious clinical features of cortisol excess. Therefore, this can cause a delay in the diagnosis of CS and these patients may be at high risk of life-threatening complications such as infections or thrombosis.
Clinical case
Case of a 70-year-old man, with recent diagnosis of small cell lung cancer was admitted for rapidly progressing hypertension, hypokalemia and severe hyperglycemia. There was no previous medical history of diabetes or hypertension. On physical examination, he did not have typical Cushingoid

features; he presented lower extremity edema and high blood pressure reaching 180/120mmHg. At admission, plasma glucose was 336mg/dl, serum potassium 2.6mmol/l, arterial pH 7.54. Cushing syndrome was suspected, and an endocrine evaluation revealed an ACTH-dependent hypercortisolism: cortisol after an overnight 1-mg dexamethasone suppression test 60.6µg/dL and ACTH 175.5ng/l. CRH stimulation test had a borderline result to differentiate the cause. Treatment with metyrapone was considered immediately and readily requested to the hospital pharmacy committee; however, there was a delay in the provision of the drug. He started emergency treatment with potassium supplementation and spironolactone. In order to use somatostatin analogs to treat the ectopic secretion, a 111-In-octreotide scan was performed, that revealed receptors in the left lung and contralateral pleura. Unfortunately, on the tenth hospital day, before any treatment for hypercortisolism was started, the patient's hospital course was complicated with a nosocomial pneumonia and the patient died.
Conclusion
Patients with ectopic ACTH secretion can be very hard to detect and typically present with a much more rapid progression compared to Cushing disease. Indeed, these patients often represent an endocrine emergency due to the intensity of their hypercortisolism. Worsening hyperglycemia in the presence of hypertension, even without typical Cushing features should prompt further hormonal work-up. To offer the patient the best chance of survival and avoid Cushing's complications such as severe infections, hypercortisolism must be controlled without delay.

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EP810

Challenges in treatment of carotid paraganglioma : About a case report

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Introduction
Carotid body tumor is a hypervascular tumor with multiple feeding arteries and unique orientation at the carotid bifurcation. Although resection is a radical therapy for this tumor, complete resection is challenging.
Case report
A 33-year-old female patient consulted with a neck swelling that had persisted for 3 years. On physical examination, a movable and pulsating hard mass was found on the left side of her neck. Computed tomography, magnetic resonance image and angiography all demonstrated a well-circumscribed tumor mass showing high vascularity and located at the bifurcation of the left carotid artery. The tumor involved the left carotid artery measuring 44 × 43X55 mm in size but the patency of the artery was preserved. The urinary catecholamines were negative. Since the tumor was strongly adherent to the carotid arterial wall, the resection was a surgical challenge and achieved due to multidisciplinary approach and cooperation with otolaryngologist and vascular surgeon. Histologically, the tumor was compatible with paraganglioma without signs of malignancy.
Discussion
Cooperation with an otolaryngologist and vascular surgeon during surgery is recommended due to frequent damage to carotid vessels by carotid paragangliomas. Detection of the tumor in the early stages improves surgical treatment outcomes and reduces the number of complications. Regular post-operative check-ups are necessary due to possible occurrences of multiple tumors.
Key-Words: Paraganglioma-Carotid body-Surgery-Risk

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EP811

A Rare Case of recurrent Hypoglycaemia

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Insulinomas, uncommon neuroendocrine tumours, may produce insulin-induced hypoglycemia. It causes neuroglycopenia and autonomic sympathetic dysfunction. Glucose immediately relieves these sensations. Hypoglycemia without plasma sulfonylurea and increased C-peptide is diagnostic. The tumour must be found before surgery.
Introduction
Hypoglycemia is caused by insulinomas. Insulinoma, the most frequent functional pancreatic tumour, occurs just four times per million. Extra-pancreatic insulinomas are rare. This unusual tumour causes sympathetic and neuroglycopenic symptoms.
Case Presentation
24-year-old boy who presented to endocrine department with recurrent episodes of hypoglycemia. This case was challenging because of the patient's history of anorexia nervosa and substance abuse. He used substances, including marijuana, cocaine, and MDMA, in the past. He had a history of at least six years of recurrent admissions to emergency care with a diminished level of awareness and seizure activity and blood glucose levels below 2.2. His symptoms recovered once his hypoglycemia was treated. Multiple studies were done to determine his symptoms because he was not diabetic. He was tested for liver, kidney, and hormonal dysfunction, such as adrenal insufficiency. In the limited supervised fast demonstrated, glucose was 1.8 mmol/l, insulin 52 pmol/l, C-peptide 795 pmol/l, beta-hydroxybutyrate less than 100 umol/l, and the IGF2:IGF-1 ratio was 2.4. Insulin antibody-negative. Negative sulfonylureas. Radiological screening proceeded. unremarkable pancreas MRI. No pancreatic lesion, especially an arterial-enhancing lesion identified. Gallium-deficient PET/CT showed no insulinoma. Endoscopic ultrasonography and biopsy were inconclusive for endogenous insulinoma.
Management
Continuous glucose monitoring equipment was supplied to check his hypoglycemia. It was difficult to control his hypoglycemia without medicine, so he began taking 150 mg of diazoxide three times a day to avoid further episodes. Further investigations are continuing. A supervised 72-hour fast was performed, which reciprocated the result of the limited fast. We chose selective calcium stimulation to locate the insulinoma. He was advised to cease diazoxide seven days before the test to prevent interference. A catheter was implanted in the right hepatic vein, proximal gastroduodenal, proximal splenic hepatic, and superior mesenteric regions. Post-calcium gluconate insulin and C-peptide levels were elevated, although we could not discern a gradient in any arterial territory to validate localization.
Recommendation
1. Consider continuing medical management, control your diet, and continue to follow up.
2. Consider an exploratory laparotomy to see if any lesion can be identified.
3. Consider partial pancreatectomy, which might be able to help with the frequency of hypoglycemia but might be tricky for iatrogenic diabetes and surgical complications.

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EP812

Adolescent Acromegaly : About 2 Case Studies

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Introduction
Acromegaly is an unusual disease in adolescence. Its diagnosis and management are a challenge in this population. Here we report 2 rare cases of acromegaly in this age group.
Patients and Observations
Observation 1: This is a 17 year old patient admitted for acromegaly on pituitary microadenoma measuring 4*3mm who presents a symptomatology made of an accentuation of the growth rate, thin and long limbs, elongated hands and feet without dysmorphic syndrome and without tumor syndrome. His GH level is 1.8 times normal and IGF1normal. Therapeutically, the patient benefited from a total removal of the tumor.
Observation 2: The patient was 16 years old and had been followed for acromegaly on pituitary macroadenoma since the age of 11 years. The initial symptomatology was an increase in growth rate without dysmorphic signs and without tumor syndrome. His IGF1 level was 2.3 times normal. The patient has already benefited from 3 surgeries of the adenoma with complementary medical treatment.
Conclusion
Adolescent Acromegaly is rare and characterized by large size and rapid progression of symptoms as the main diagnostic criteria. Other clinical signs are less marked than in adults. Surgery is the first-line treatment with importance of long-term follow-up.

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EP813

Craniopharyngioma masquerading as a suprasellar Rathke cleft cyst in a young patient with a history of Ewing sarcoma: A case report

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Craniopharyngiomas are rare, benign tumors, typically found in childhood or early adulthood, that can cause a wide range of symptoms such as visual impairment, headaches, nausea and endocrine disturbances. Ewing sarcoma, on the other hand, is a rare and aggressive tumor that arise from primitive neuroectodermal cells and represents about 10% of all pediatric osseous primary tumors. We present the case of a 14-year-old patient who was admitted to our clinic in March 2022 for obesity, secondary amenorrhea and visual impairment. The patient was diagnosed at the age of 11 with Ewing sarcoma of the lumbar spine with left intracanal extension L5-S1. She had received concomitant local radiotherapy (45Gy per 25 fractions) and chemotherapy (8 cycles of Vincristine, Ifosfamide, Doxorubicin, Etoposide) according to Ewing Protocol from 2008. The patient experienced her first menarche 2 months after the first cure of chemotherapy, followed by one additional menstrual cycle at a two-month interval, with secondary amenorrhea since. In July 2020, she experienced a seizure and visual disturbances. Cerebral MRI showed a suprasellar cystic mass measuring 1.6/1.3/1.5cm, causing optic chiasm compression, first diagnosed as a Rathke cleft cyst. The patient began anticonvulsant treatment and continued to receive regular follow-up care. During the patient's first presentation in our clinic, laboratory evaluation revealed elevated follicle-stimulating hormone levels (35.30mIU/ml) with low estradiol levels (13.18 pg/ml) and AMH levels (0.01ng/ml) suggesting primary ovarian failure due to radiotherapy and chemotherapy. Thyroid function was also modified, suggesting hypothyroidism due to autoimmune thyroiditis. Ophthalmologic evaluation revealed right homonymous hemianopia. The 2-year follow-up MRI showed unchanged dimensions of the suprasellar mass, impingement on the optic chiasm. Unfortunately, according to the neurosurgeon the mass was highly suggestive for a craniopharyngioma requiring surgery if the visual impairment intensified. Taking in consideration the fact that our patient had a history of epilepsy, we initiated sex hormone replacement therapy with low doses of estrogens, progestin and levothyroxine. In conclusion, we report a rare association between Ewing sarcoma, an aggressive bone and soft tissue tumor and craniopharyngioma, a benign, intracranial tumor, both requiring complex and challenging management by a multidisciplinary team due to significant long-term morbidities caused by their treatment and the loco-regional tumor growth. A lifetime follow-up is necessary to address multiple endocrine deficits, that may adversely affect fertility, growth or thyroid function, highly influencing the quality of life.

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EP814

Short stature caused by pituitary stalk interruption syndrome in a type 1 diabetic child: a case report

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Introduction
Pituitary stalk interruption syndrome is a rare disorder characterized by a specific tirade: an absent or hypoplastic anterior pituitary gland, thin or absent infundibulum, and ectopic posterior pituitary location. This syndrome has been described in association with other somatic abnormalities and recently a polygenic etiology has been suggested. Herein, we report a case of type 1 diabetic patient, explored for short stature, revealing a pituitary stalk interruption syndrome.
Case presentation
We report the case of an 8-year-old patient, with a medical history of type 1 diabetes since the age of two. During his follow up, stature delay has been noticed but initially put on the account of diabetes. At the age of eight, he consulted our endocrinology department. Physical examination showed a height of 110 cm which was below the second percentile for chronological age, and weight was 23 kg which was at the third percentile. Bone age was five years according to the Greulich and Pyle method. Biological analysis revealed an HbA1c level of 7,5%. First line investigation, including complete blood count, creatinine and liver enzyme was normal. Antitissue transglutaminase, anti-endomysium, and anti-gliadin antibodies were negative. The hormonal investigation showed a normal thyroid function test (TSH level of 1.35 mIU/l and free thyroxine of 10.9 pmol/l). The diagnosis of corticotropic insufficiency was confirmed by a low baseline plasma cortisol level (168 nmol/l) unstimulated by Insulin-induced hypoglycemia test and low adrenocorticotropin hormone (ACTH) level. IGF1 levels were 82 ng/mL which was normal for age. The diagnosis of GH deficiency was retained based on no GH response to two stimulation tests: Insulin-induced hypoglycemia and clonidine tests. Pituitary MRI showed the typical triad of pituitary stalk interruption syndrome. The patient was treated with hydrocortisone and recombinant GH replacement therapy with good evolution of stature.
Conclusion
Pituitary stalk interruption syndrome should be kept in mind while investigating a child with short stature, even if patient history suggests other etiologies. The pathophysiology of this syndrome is not yet fully understood, but it has been described in association with several diseases and appears to be polygenic.

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EP815

Desmopressin or decompensated corticotropic insufficiency: who is the guilty party in profound hyponatremia?

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Introduction
We report the case of a patient with corticotropic insufficiency associated with diabetes insipidus who presented to the emergency room with profound hyponatremia; a complicated situation, whose solution was hidden in the galenic form of Desmopressin.
Case report
Mrs Y. Amina, 37 years old, has been followed for 10 years for a non Langerhansian histiocytosis of pituitary location, complicated by a corticotropic insufficiency under hydrocortisone, and a diabetes insipidus under inhaled desmopressin, consulted in the emergency room for a confusional syndrome associated with nausea, vomiting and abdominal pain, the assessment carried out in urgency showed a deep hyponatremia at 118 mEq/l. This situation led to the suspicion of a decompensation of corticotropic insufficiency and the patient was put on intravenous hydrocortisone hemi succinate. The evolution was marked by the persistence of hyponatremia and the installation of hypokalemia which worsened progressively, thus signalling a corticosteroid overdose and the theory of a decompensation of corticotropic insufficiency was questioned in favor of another possibility; Desmopressin overdose, a reduction in the dose of this drug was considered, from 2 puffs per day to one puff per day, the natremia thus went to 124 mEq/l, and remained stationary. Our decision was to change the galenic form of the drug, and the patient was put on Desmopressin tablet (1 tablet in the morning and 1 tablet in the evening), the evolution was favorable with correction of the natraemia and disappearance of the symptoms.
Discussion
Used to prevent or control symptoms of central diabetes insipidus, Desmopressin is a synthetic analog of arginine vasopressin. It is more potent and much longer acting than vasopressin. Hyponatremia is a classic complication of desmopressin overdose, usually corrected by dose reduction, but in some cases, individual sensitivity is so great that even small doses can cause overdose effects. It is at this point that it is necessary to think about changing the dosage form, as the bioavailability of desmopressin varies considerably from one dosage form to another, and the fact of changing, in our case from the potent inhaled form to the oral form, has made it possible to reduce the bioavailability of the molecule.
Conclusion
In situations similar to ours, when inhaled desmopressin is at its lowest dose, we suggest changing the galenic form in order to reduce the bioavailability of the drug and thus make the adverse effect beneficial.

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EP816

A Rare Pituitary Pathology: Patient With Crooke Cell Corticotroph Adenoma

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However ACTH secreting adenomas are one of the most common functional pituitary tumors, subtypes such as Crooke cell corticotroph adenoma(CCCA) are relatively rare. We present here a patient with CCCA who had severe hypercortisolism mimicking ectopic ACTH syndrome. A 69 years old female

patient admitted to emergency department after a fall. On cranial MRI,'a 3.5x2.5x3cm mass appearance with a sellar-suprasellar location, which is compressing the optic chiasm, expanding the sella to cavernous sinuses' was detected. It was learned that she gained weight in the last year and his blood sugar had been dysregulated. She had a buffalo hump, thin extremities and central obesity. No signs of abdominal wall striae, facial plethora and proximal myopathy were observed. The biochemistry and anterior pituitary hormone examination results are as in Table 1. The result of 1 mg dexamethasone suppression test was 43.56μg/dl. The midnight serum cortisol was found to be 33μg/dl, the midnight salivary cortisol was 2.24μg/dl and 24 hours urinary free cortisol level was 1718,35 mg/24 h. Spironolactone and metyrapone were started due to resistant hypokalemia and overt hypercortisolemia. In the multidisciplinary council; surgery was decided. After transsphenoidal surgery, focal staining with ACTH and thick membranous staining in more than 50% of cells were detected in the operation material. Pathology result was reported as compatible with CCCA. Metyrapone was discontinued in the post-operative period. The patient who developed central hypothyroidism and central diabetes insipidus was started on levothyroxine and desmopressin treatments. Hypercortisolemia could not be evaluated in the post-operative period;because after the surgery, dexamethasone was given to the patient with subdural hematoma secondary to falling, for anti-edema effect. CCCA are rarely seen tumors. They tend to be invasive and clinically aggressive. They may recur after surgery and may show resistance to re-operation or radiotherapy(1). In our case;there was a pituitary mass pressing on the surrounding tissues, severe hypercortisolemia and rapid progression of clinical and laboratory findings mimicking ectopic ACTH syndrome.

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Table 1 Results of biochemistry and anterior pituitary hormone tests.

Glucose	**265mg/dl**	TSH(0,55-4,78mU/l)	1,14mU/l
Hba1C(<%5,7)	**%9,9**	Free T4(0,89-1,76 ng/dl)	1,18ng/dl
ACTH(<46 μg/dl)	**68,0μg/dl**	Free T3(2,3-4,2 ng/l)	2,63ng/l
Cortisol(5.2-22.4 μg/dl)	**53,7μg/dl**	**IGF-1(65-200 μg/l)**	**61μg/l**
FSH(post-menopausal 23-116.3U/l)	**0,9U/l**	Growth Hormone(0,05-8 μg/l)	0,1μg/l
LH(post-menopausal 15,9-54U/l)	**<0,07U/l**	Sodium(132-146 mEq/l)	139mEq/l
Estradiol(post-menopausal< 32,2ng/l)	<11,8ng/l	**Potassium(3,5-5,5mEq/l)**	**3,1mEq/l**
Prolactin(post-menopausal 1,8-20,3μg/l)	2,7μg/l	Creatinine(0,7-1,3mg/dl)	0,51
		ALT/AST(<50/<35U/l)	84/26U/l

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EP817

Contribution of MRI to the diagnosis of hypophysitis

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Introduction

Hypophysitis is a rare condition corresponding to a chronic inflammation of the pituitary gland, The clinical and radiological signs are not specific and the pathogenesis remains poorly elucidated. The aim of our work is to report the clinico-radiological aspects of hypophysitis.

Material and Methods

This is a retrospective descriptive study of 09 patients hospitalized in the department of Endocrinology-Diabetology-Nutrition of Mohammed-VI University Hospital Center, Oujda, over a period of 5 years who were diagnosed with hypophysitis. All our patients underwent hypothalamic-pituitary MRI. Data were collected from medical records and analyzed by SPSS-V21 software.

Results

The age of our patients ranged from 16 to 49 years, 6 were female. One patient was in immediate postpartum, 3 other patients were already being followed for autoimmune diseases : a Hashimoto disease, a coeliac disease and a lupus. A COVID-19 infection was found in one patient. Polyuro-polydypsia syndrome was the main revealing sign, associated in one case to clinical signs secondary to mass effect and in another case to signs of hypopituitarism. MRI showed a diffuse enlargement of the pituitary gland in 5 cases, a thickened pituitary stalk in 2 cases, markedly homogeneous contrast enhancement of the pituitary gland in 2 cases. Loss of posterior pituitary bright spot was observed in 3 patients. A lymphocytic autoimmune origin was retained in 6 patients. Infiltration of the gland by a tuberculous granuloma was retained in a single case with a good clinical evolution under treatment.

Discussion-conclusion

Hypophysitis is a rare pathology of the pituitary gland that predominates in young women. It is often manifested by hypopituitarism or visual disorders simulating a pituitary adenoma. MRI allows the diagnosis to be suspected by showing an intra- and extra-sellar mass, symmetrical, taking the contrast in a homogeneous way, which is associated during infundibulo-neurohypophysitis to a thickening of the pituitary stem as well as the loss of the spontaneous bright-spot reflecting the absence of vasopressin storage at this level. Its interest is primordial in the diagnosis and the control of the evolution of lymphocytic and granulomatous hypophysitis.

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EP818

A Pituitary Neoplasm with an Aggressive Course: Silent Corticotroph Adenoma

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Patient is a 43 years old female without any known additional disease. A pituitary mass was seen in the cranial MRI taken due to the complaint of forgetfulness. Pituitary MRI of the patient revealed a 'large intrasellar mass of 3.2x3x2.3 cm, which expanded the sella and pressed the optic chiasm'. The patient didn't describe any symptoms other than forgetfulness. She didn't have galactorrhea, cushingoid or acromegaloid appearance. Patients laboratuary evaluation can be seen in Table 1. The patient was started on levothyroxine for central hypothyroidism and it was thought that the patient had a non-functional pituitary adenoma. In the follow-up of the patient who underwent transsphenoidal surgery, no hypopituitarism or central diabetes insipidus was detected. In the immunohistochemical and histological examination of the patient's surgical material:'Tumor cells showed diffuse staining with ACTH. GH, PRL, TSH, FSH, LH are negative. The Ki-67 proliferation index was 3-4%.'These findings, patient's pre-operative examinations and clinically situation were evaluated and it was determined that the patient had a 'silent corticotroph adenoma'. The patient had no complaints in the post-operative first month. Her anterior pituitary hormones were observed(Table 2). Due to the tendency of silent corticotroph adenomas to progress aggressively, pituitary MRI control was planned at the post-op 3rd month. Silent corticotroph adenomas constitutes 4.8-6.8% of all pituitary adenomas and 19% of non-functioning pituitary adenomas. It has a highly aggressive and invasive course. It often recurs after treatment and is resistant to treatment. In the studies,0.5 mg DST performed with a cut-off value of 3.0μg/dl in the screening of Cushing's syndrome. That has been shown to have higher sensitivity and specificity than the classical 1 milligram DST. In our case, both screening tests were applied.

Table 1 Biochemistry and pre-operative anterior pituitary hormone examination results.

Glucose	83mg/dl	TSH(0,55-4,78 mU/l)	0,90mU/l
ACTH(<46pg/mL)	17,3μg/dl	**Free T4(0,89-1,76 ng/dl)**	**0,75ng/dl**
Cortisol(5.2-22.4μg/dl)	16,6μg/dl	**Free T3(2,3-4,2 ng/l)**	**2,20ng/l**
FSH(post-menopausal 23-116.3U/l)	**9,0U/l**	IGF-1(65-200 μg/l)	133μg/l
LH(post- menopausal 15,9-54 U/l)	**2,1U/l**	Growth Hormone(0,05-8μg/l)	1,4μg/l
Estradiol (post- menopausal<32,2ng/l)	27,0ng/l	Sodium(132-146mEq/l)	141mEq/l
Diluted Prolactin(2,8-29,2 μg/l)	28,57 μg/l	Potassium(3,5-5,5mEq/l)	4,1mEq/l
1 milligram DST(<1,8μg/dl)	1,6μg/dl	Urinary density(1003-1030)	1022

Table 2 Biochemistry and anterior pituitary hormone test results in post-operative first month

Urinary density(1003-1030)	1014	TSH(0,55-4,78mU/l)	2,60mU/l
ACTH(< 46pg/mL)	**49,6 μg/dl**	Free T4(0,89-1,76ng/dl)	0,98ng/dl
Cortizol(5.2-22.4μg/dl)	**25,3μg/dl**	Free T3(2,3-4,2ng/l)	2,35ng/l
FSH(post-menopausal 23-116.3U/l)	**7,1U/l**	IGF-1(65-200μg/l)	150μg/l
LH(post- menopausal 15,9-54U/l)	**1,6U/l**	Growth Hormone (0,05-8μg/l)	0,7μg/l
Estradiol(post- menopausal < 32,2 ng/l)	25,0ng/l	Sodium(132-146mEq/l)	141mEq/l
Prolactin(post- menopausal 1,8-20,3μg/l)	**34,1μg/l**	Potassium(3,5-5,5mEq/l)	3,8mEq/l
1 milligram DST(< 1,8μg/dl)	1,04μg/dl		
0,5 milligram DST(< 3μg/dl)	0,90μg/dl		

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EP819

Noonan syndrome associated with SOS1 gene mutation with autosomal dominant RASopathy : a case report

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Introduction
Noonan syndrome (NS) is an autosomal dominant genetic disorder characterized by the combination of facial dysmorphia, short stature and congenital heart disease. The mutation of the PTPN11 gene is present in 50% of cases, recently the mutation of other genes was found, notably KRAS and SOS1. We report the case of a patient followed in our department for NS with a SOS1 gene mutation.
Case report
A 4 years old male patient, referred to our department for failure to thrive (FTT). The diagnosis of NS was made in view of a typical facial dysmorphia, a congenital cardiac disorder with a moderately tight pulmonary valve stenosis, a bicuspid aortic valve and a non-stenosing sub-aortic septal hypertrophy for which the patient was operated, as well as a FTT with a weight and a height between - 2 and - 3 standard deviation (SD). A left cryptorchidism was also found on clinical examination. The genetic study found a pathogenic variant of the SOS1 gene with autosomal dominant RASopathy. For his FTT, the first line workup was normal. IgF1 was normal for the age of the patient. The glucagon test wasn't in favor of growth hormone (GH) insufficiency.
Discussion and conclusion
At present, seven genes have been shown to be associated with NS: PTPN11, SOS1, RAF1, KRAS, NRAS, SHOC2, and CBL. The most common gene associated with NS is PTPN11, which accounts for approximately 50% of all cases. SOS1 missense mutations are the second-most-common cause of NS, accounting for approximately 15% of cases. NS is one of a group of genetic diseases called RASopathies. They are clinically defined as a group of medical genetic syndromes caused by germline mutations in genes that encode components or regulators of the Ras-mitogen-activated protein kinase (MAPK) pathway. These disorders include neurofibromatosis type 1, Noonan syndrome, Noonan syndrome with multiple lentigines, capillary malformation–arteriovenous malformation syndrome, Costello syndrome, cardiofaciocutaneous syndrome, and Legius syndrome. They have in common many symptoms. In our patient, Costello syndrome was also discussed as a diagnosis, but we did not find an abnormality of the HRAS gene.

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EP820

Delayed diagnosis of idiopathic growth hormone deficiency in children

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Background
The delay of diagnosis of idiopathic growth hormone deficiency (GHD) in children, would result in delayed management, and would significantly affect final adult height.
Methods
This was a retrospective chart review study for patients seen at the pediatric endocrine clinic at the Jordan University Hospital, over a period of six years. Demographic, clinical, auxological and hormonal characteristics were studied.
Results
There were 87 patients diagnosed with idiopathic GHD, where there were no identified etiology, out of those patients 50 (57.5%) patients were males. Average age at presentation was 9.40 ± 2.90 years and 86.2% were pre-pubertal at presentation. The mean height standard deviation score (SDS) was -2.97 ± 1.02, while mid-parental height SDS was -0.98 ± 0.67. Mean bone age delay was 2.73 ± 0.70 years and insulin growth factoe-1 was 107.0 ± 89.1 ng/ml. There was history of consanguinity in 28 (32.2%) patients, this relatively higher percentage of consanguinity would suggest that there were underlying genetic disorders which were not identified for lack of genetic testing in developing countries.
Conclusion
Diagnosis of idiopathic growth hormone deficiency in children in Jordan was relatively delayed, which results in delayed management and would affect negatively final adult height. Close follow up for growth in children should be an integral part of primary health care systems including developing countries, where such practice may be sub-optimal. Abnormal growth warrants early referral to pediatric endocrinology service for early diagnosis and management.

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EP821

Comparison between insulin tolerance test and clonidine stimulation test in the exploration of growth hormone deficiency

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Introduction
Growth hormone deficiency (GHD) is a rare cause of delay of growth. However, it is primordial to screen for it since its presence leads to a specific treatment which improves statural prognosis. GHD should be confirmed through stimulation tests such as Insulin Tolerance test (ITT) or Clonidine Stimulation Test (CST). The objective of our study was to compare these two diagnostic tools.
Methods
We conducted a retrospective study in the endocrinology service of the military hospital of Tunis that involved 25 patients who were referred to our department for exploration of growth delay. The GH responses of participants were compared according to the test used (ITT or CST). GHD was retained if GH $<$ 10 ng/mL. A severe GHD was retained if GH $<$ 05 ng/mL.
Results
The mean age of the sample was 12 $\pm$ 3 years with male predominance (80%). Almost half of the sample (46%) had a clinical severe growth delay. GH peak during ITT was 2.12 $\pm$ 1 vs 4.09 $\pm$ 3 during CST ($P = 0.08$). When using ITT, the majority of participants 94% had severe GHD, while only 60 % presented severe GHD if CST was used ($P = 0.04$).
Conclusion
ITT seems to be significantly more sensible in the exploration of the somatotropic axis

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EP822

Polyuria-polydipsia syndrome revealing primary potomania : a diagnostic challenge

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Introduction
Polyuria-polydipsia syndrome (PUPDS) requires a comprehensive diagnostic approach as it can reveal serious medical conditions. We report the case of a patient consulting for PUPDS related to a primary potomania.
Case presentation
A 41-year-old patient with a history of multiple psychostimulants use was admitted for acute PUPDS after emotional shock and paucisymptomatic SARS-CoV-2 infection. Diuresis was estimated at 6 liters per 24 hours. During the interview, the patient reported psychostimulants withdrawal for over a year. He

did not have tumor syndrome. Urinary density was <1005. A brain MRI was performed showing persistent hyperintensity on T1-weighted image of the posterior pituitary, ruling out a diagnosis of central diabetes insipidus. However, this diagnosis was not entirely ruled out by the hypothesis of acute-onset ADH deficiency due to COVID-19 infection. Given the importance of PUPDS, the patient was given desmopressin with marked clinical improvement. A Fluid deprivation test was done two months later. The patient concentrated his urine and ADH level was normal. Therefore the diagnosis of primary potomania was maintained and the patient was referred to psychiatric clinic.
Discussion:
Primary potomania is a psychopathology that represents a differential diagnosis with diabetes insipidus and remains a diagnosis difficult to maintain until another organic cause is ruled out.

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EP823

Wolfram Syndrome: Case report

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Background
Wolfram syndrome is an autosomal recessive neurodegenerative disease. It is secondary to the mutation of WFS1 gene. It combines a tetrad of pathologies known also as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness).
Case presentation
We report a case of 31-year-old women with medical history of type 1 diabetes since the age of 3 years old. She suffered from decreased visual acuity since the age of 5 years old and the ophthalmological examination showed an advanced bilateral optic atrophy with no signs of diabetic retinopathy. She experienced many episodes of urinary tract infections and urologic examination and ultrasound findings were consistent with a neurogenic bladder. She recently consulted for polyuria and polydipsia and the dehydration test confirmed the diagnosis of diabetes isipidus. The diagnosis of Wolfram syndrome was highly suspected and a genetic study was done searching for the WFS1 mutation.
Conclusion
Wolfram syndrome should be considered in patients with diabetes mellitus and optic atrophy, which are the first signs of the disease. The condition should be evaluated in a multidisciplinary manner and specific tests are necessary to make a precise diagnosis and disclose all components of the syndrome in order to improve patients' prognosis.

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EP824

A case of a persistent hypernatremia secondary to adipsic central diabetes insipidus

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Introduction
Central diabetes insipidus is a rare condition that typically manifests as polyuria-polydipsia syndrome. Polydipsia helps to maintain normal natremia. Herein, we report the case of persistent hypernatremia in a patient admitted for inaugural diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome.
Observation
A 53-year-old woman was referred to our department for inaugural diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome. Her past medical history included herpetic meningoencephalitis complicated by confusion, amnesia, and adipsia. On physical examination, she was apyretic, hemodynamically stable, and confused with signs of isolated extracellular dehydration. Laboratory investigations showed hyperglycemia at 30 mmol/l, hypernatrémie at 169 mmol/l with a plasma hyperosmolarity at 386.3 mOsm/l. The patient received rehydration with isotonic saline solution and insulin therapy. Ketosis was controlled with normalization of blood glucose. However, hypernatremia persisted (148-158 mmol/l) as much as the hyperosmolarity (321-336). Urine output was quantified at one liter/24h. Natriuresis was 54 mmol/l and urinary osmolarity was 205 mOsm/l suggesting hypotonicity. After administration of desmopressine, the natriuresis normalized and the urinary osmolarity rose to 743 mOsm/l. The diagnosis of central diabetes insipidus associated with adipsia was established and the patient was treated with desmopressine. The pituitary hormonal investigation showed isolated central hypothyroidism. Pituitary magnetic resonance imaging was normal.
Conclusion
Our case describes an uncommon presentation of central diabetes insipidus with no polyuria. The impaired sensation of thirst may be responsible for an atypical presentation of central diabetes insipidus called hypernatremia-hypodipsia syndrome.

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EP825

Pituitary cystic images: difficult diagnosis

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Introduction
The most frequent cystic lesions in the pituitary region are: cystic adenomas, Rathke's pouch cysts and craniopharyngiomas. But sometimes the diagnosis can be difficult.
Clinical case
This is the case of a women patient who consulted at the age of 20 for a pituitary cystic process revealed by secondary amenorrhoea; evoking in the first place a Rathke's pouch cyst. Hormonal assessment reveals tumour-related hyperprolactinemia; the diagnosis of cystic prolactinoma is evoked. It is the response to anti-dopaminergic medical treatment and the morphological response to MRI that leads to the diagnosis of a probable cystic prolactin adenoma.
Conclusion
A radiological image can only be interpreted with caution because it is the set of clinical and biological characteristics that allow a definitive diagnosis to be made.

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EP826

Cushing's disease in children: review of 3 cases

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Introduction
Cushing's disease is defined as hypercortisolism caused by excessive secretion of ACTH from a pituitary adenoma. Cushing's disease is a rare entity in children
Observation
We report the case of 3 children with Cushing's disease including 2 boys and 1 girl, the mean age at the diagnosis was 12.6 years. Clinically, weight gain was constant in all children, a delay in statural growth was noted in 2 children, signs of catabolism were found in one child. Biologically, the hormonal exploration reveal an ACTH-dependent hypercorticism Morphologically, the adenoma was visualised on MRI in one patient; however, the size of the adenoma was 4 mm requiring petrous sinus catheterisation. Petrous sinus catheterisation was used in all our children; this examination objectified a Centro peripheral gradient in 2 cases; but was non-contributory in the 3rd child. In terms of treatment: only one child with very severe cushing's disease was operated by transphenoidal approach on 3 occasions with failure, requiring bilateral adrenalectomy complicated by Nelson's syndrome, treated with radiotherapy and dostinex. The other 2 children are currently awaiting pituitary surgery and are on anticortisol therapy.
Discussion
Endogenous cushing's syndrome in children is rare, the most common cause remains cushing's disease. Often, in these children, the tumours are very small and cannot be detected on MRI. Despite the difficulty of this delicate procedure, petrosal sinus catheterisation was able to make the diagnosis in two out of three children.
Conclusion
Cushing's disease in children is rare;. Its management represents a real challenge requiring the use of a specialised multidisciplinary team

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EP827

Resistant to treatment prolactinoma: report of two cases

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Introduction
Prolactin-secreting tumors or prolactinomas comprise the most common pituitary tumor type, acconting of 47-66% of all pituitary tumors. These tumors can be treated with dopaminergic drugs (DA) however 10-15% of prolactinomas are DA resistant.
Case 1
A 39 years old man followed for a geant agressif prolactinoma discovered following a progressive decline in visual acuity and associated with visual impairment (diplopia), the MRI of the sellar region (magnetic resonance imaging) (Figure1) had shown a voluminous endosellar process. Hormonal work-up revealed a serum prolactin level of 174,8 ng/ml and pituitary deficiencies. The ophthalmic examination found bitemporal hemianopia. The patient was then started on dopamine agonist (cabergoline 02mg/week). Two months later, the patient consults at the emergency unit for vomiting, headaches and reduced visual acuity, suggestive of apoplexy. The MRI reveals a clear increase in the sellar process at the expense of the sellar portion wich fills the entire optochiamatic citern, lifting and compressing the optic chiasm and reaching the Monro holes with the onset of dilatations of the lateral ventricles, the patient had a transphenoidal partial adenomectomy. The histological analysis confrmed a PRL tumor classified grade IIb Trouillas 2013 and the Ki67 was 12%. The MRI related two months later showed a slight tumor reduction (24x43x29mm) so the dopamine agonist was continued at the dose of 3,5mg/week. Three months later; the MRI demonstrated an increase in volume, the decision for chemo-radiotherapy such as the STUPP protocol (radiotherapy associated to 75mg/m2 of Tomozolomide). Suddenly our patient died one moth later during the Covid 19 pandemia.
Case 2
A 37 years old women followed for a resistant prolactinoma discovered following a galactorrhea and spaniomenorrhea. Hormonal work-up revealed a serum prolactin level of 292,9 ng/ml without pituitary deficiencies and the MRI of the sellar region had shown a macroadenoma. The patient was then started on dopamine agonist (cabergoline 0,5mg/week with gradual increase in doses up to 3,5mg/week. The hormonal control was never obtained and the MRI shown a 50% increase. The patient had a transphenoidal adenomectomy.
Conclusion
Prolactinomas are the most prevalent functioning pituitary adenomas and the easiest to treat by endocrinologists, being in the majority of cases responsive to medical treatment with DAs. However, up to 15% of cases are resistant, locally invasive and depict an aggressive growth pattern.

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EP828

Panhypopituitarism of unknown aetiology in a young adult – a case report

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Introduction
Hypopituitarism is a rare diagnosis that is mainly due to primary pituitary neoplasms and their treatment. There are rarer causes such as hemorrhage/ischemia, traumatic brain injury, infections and infiltrative lesions.
Clinical case
We herein present an 18-year-old male patient diagnosed with acute promyelocytic leukemia at the age of 14, with no evidence of central nervous system invasion in several lumbar punctures during his follow-up. He was treated with chemotherapy (without cranial radiotherapy), being in remission for 10 months before he presented to the Endocrinology Clinic due to thyroid dysfunction: TSH 0.15 (0.27-4.20) uUI/mL and FT4 0.69 (0.80-1.67) ng/dl. He was asymptomatic, with a height of 164 cm (family target height of 167 cm) and pubertal Tanner stage 4. A second blood sample revealed a TSH of 5.32 (0.27-4.20) uUI/mL and a FT4 of 0.41 (0.80-1.67) ng/dl. Facing the suspicion of a central hypothyroidism, a pituitary panel was requested, showing low cortisol levels [1.68 (5.0-25.0) mg/dl with an inappropriately normal ACTH, a slightly high prolactin [54.4 (4.04-15.20) ng/ml], low IGF1 [60.1 (132-476) ng/ml (z-score -3.39)] and a low total testosterone leves [231 (300-1200) ng/dl] (calculated free testosterone of 3.87ng/dl). FSH and LH were normal. He was sequentially started on hydrocortisone 15 mg/day, levothyroxine 100 mg and testosterone 250 mg every 6 weeks. Brain MRI was performed and showed a discrete thickening of the pituitary stalk, measuring 4mm, with signal enhancement after gadolinium contrast, which had been known for at least 3 years. Hemochromatosis and plasmacytic hypophysitis were ruled out considering normal iron kinetics and IgG4 levels. Currently, the patient remains in leukemia remission, undergoing replacement therapy for three of the affected pituitary axes, and considering supplementation with growth hormone.
Conclusion
In this case, the laboratorial and imaging studies have not unequivocally identified the cause of hypopituitarism. Genetic combined pituitary hormone deficiency syndromes are unlikely considering his age at diagnosis, his height and normal puberty development. Pituitary leukemic infiltration remains a diagnostic hypothesis despite its rarity and considering that central nervous system involvement has never been documented in the several lumbar punctures that were performed.

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EP829

Central diabetes insipidus caused by a Lymphocytic infundibuloneurohypophysitis

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Lymphocytic infundibuloneurohypophysitis (LINH) is rarely reported due to lymphocyte infiltration in the neurohypophysis. Causes of central diabetes insipidus include idiopathic diabetes insipidus (DI), primary or secondary tumors or infiltrative diseases (such as Langerhans cell histiocytosis, lymphocytic hypophysitis), neurosurgery and trauma.
Case
A 59-year-old female patient presented with complaints of fatigue for 1 month, dry mouth and drinking a lot of water. In the blood tests of the patient, Serum glucose: 97 mg / dL (70-100), Blood urea nitrogen: 35 mg / dL (6-20), creatinine: 0.7 mg / dL (0.7-1.2), sodium: 152 mmol / L (136-145), potassium (K): 4.8 mmol / L (3.5-5.1), hemoglobin: 14.6 g/dl (12.6-17.4), CRP: 8 mg/l (<5), TSH: 2.2 µIU/mL (0.2-4.2), free T4: 1.2ng/dl (0.9-1.7), cortisol: 11 mg/dl (6-18), FSH: 29 mIU/mL (1.5-13), LH : 16 mIU / mL (1.7-8.6), ACTH: 15 ng/l (7-63), prolactin: 30 µg / L (5-10), Ca: 9 (8.6-10 mg/dl), Parathormone: 54 (N: 15-65 pg/ml), ESR: 26 mm (2-20), HbA1c: 5.7%, ANA and ANCA profile: negative, ACE: 23 U/l (13-63), Plasma osmolality : 313 mOsm/l, urinary osmolality: 124 mOsm/l, urine density : 1003. At the 6th hour of the water restriction test, the patient lost 600 g of weight, the urine output decreased by 50cc, the urine density increased to 1009 and sodium to 167 mmol/l. There was a 15% increase in urine osmolality after desmopressin. In the patient's pituitary MRI, the infindibulum was thick and the hyperintensity of the neurohypophysis disappeared in T1 sequence. Nothing was found in the examinations performed for malignancy screening and colonoscopy. The patient was diagnosed with partial central DI due to Lymphocytic infundibuloneurohypophysitis. In our case, clinical diagnosis was made without biopsy. Since the patient did not have deficiencies in other pituitary hormones, treatment with only desmopressin 10 µg intranasal spray was continued.
Conclusion
Although Lymphocytic infundibuloneurohypophysitis is rare, it should be kept in mind in the differential diagnosis of patients presenting with central diabetes insipidus.
Key words: Lymphocytic infundibuloneurohypophysitis, Diabetes insipidus

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EP830

Two diabetes insipitus cases due to Langerhans cell histiocytosis

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Introduction
Langerhans cell histiocytosis (LCH) is a neoplastic histiocytic disorder that characterized by proliferation of abnormal Langerhans cells. The most typical organs affected by LCH are the skin and bones, though it can also affect the pituitary gland, central nervous system, liver, spleen, lungs, and other organs.

Case 1
36 year old man presented with polyuria, polydipsia and right hip pain lasting about 4 months. The pain increased in the last month. MRI of the hip resulted as lytic bone lesions. To further investigate a PET/CT was performed. PET/CT scan showed the patient had multiple lytic lesions on his left scapula, left maxilla, right 7-8-9th costae, T10-L1 vertebrae, sacrum, right iliac, right acetabular joint, and left ischium. A biopsy from one of the lytic bone lesions pathology is reported as LCH. In the fluid deprivation procedure, repeated urine tests showed no increase in the urine density, therefore the patient accepted as Central Diabetes Insipitus (CDI). The patient was prescribed 120 mg nasal desmopressin. Tests were not compatible with pituitary insufficiency. MRI of the pituitary revealed histiocytosis and stalk invasion. The patient recieved 12 cycles of cytarabine, 6 cycles of high-dose methotrexate and vemurafenib 2 x 960 mg as chemotherapy.
Case 2
35 year old man presented with polyuria, polydipsia and was diagnosed as CD at 2016 and prescribed 2x120 mg nasal desmopressin. The patient reported back discomfort and jaw pain during the subsequent appointments in 2018 and 2019, respectively. In the year 2020 the pathology result of the molar tooth and mandibula came as LCH. The patient recieved six cycle of vinblastine and prednizolon as the initial chemotherapy. After 5 months of drug-free follow up, radiotherapy was administered to the iliac bone, right shoulder and mandibula. The patient's symptoms do not improve in the following six months, and this is considered as disease progression. The patient then recieved eleven cycle of vinblastin 10 mg in the year 2021. The most recent PET/CT scan revealed remission of the illness. His pituitary functions were not compatible with pituitary insufficiency.
Discussion
Despite its rarity, LCH should be considered when making a differential diagnosis for patients who have central diabetes insipidus.
Key words: Langerhans cell histiocytosis, Central Diabetes Insipitus
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EP831

Pituitary Abscess – A challenge to diagnose preoperatively
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Background
Pituitary abscess is rare but a serious intrasellar infection. It should be considered in the differential diagnosis of the sellar masses due to its high morbidity and mortality rates. Despite recent advances in radiological investigations, it remains a challenge to make a definitive diagnosis preoperatively [1]. We present a case of pituitary abscess who presented with pan hypopituitarism and central diabetes insipidus.
Case presentation
A 34-year-old man with no significant past medical history was referred to the medical unit with a low serum cortisol (14 nmol/l). He had a 3 month history of fatigue, polyuria, polydipsia, cold intolerance and reduced libido, as well as a 1 week history of frontal headache worse with coughing and movement. No visual disturbances were present. Clinical examination and observations were normal. Routine blood tests revealed no electrolyte abnormalities with mild leucocytosis. Further investigations demonstrated pan hypopituitarism with secondary adrenal insufficiency, central hypothyroidism, and secondary hypogonadism. Central diabetes insipidus was suspected. Hydrocortisone, levothyroxine and testosterone were started initially, then desmopressin added due to ongoing polyuria, all with good symptomatic effect. MRI pituitary with contrast showed a 13x9mm lesion with peripheral enhancement and cystic-like component within the pituitary gland. Following referral to the pituitary MDT, he underwent endoscopic trans-sphenoidal pituitary surgery where pus was noted in the pituitary fossa. Drainage of the pituitary abscess was performed. Pus samples grew *Staphylococcus aureus*. He was treated with intravenous cefotaxime then switched to oral linezolid for a total of 4 weeks' treatment. Post-operative MRI showed reduction in the cystic pituitary lesion. Patient remained on hormone replacement therapy.
Conclusion
To conclude we can say that, despite rarity of the condition and radiological uncertainty, the history of recent infection or surgery of nearby structures or immunosuppression makes it highly suspicious of pituitary abscess. Although these risk factors were not apparent in our case. Prompt surgical drainage of the abscess followed by prolonged antibiotic therapy and hormonal replacement remains the main stay of treatment [2].
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EP832

An Atypical Presentation of Hypopituitrism
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A 48-year-old male presented with headache, cough and recurrent nose bleeds. Clinical examination showed saddle shape nose deformity. His past medical history included primary hypothyroidism diagnosed at the age of 10 years, was taking levothyroxine. His brother had a Rathke's cleft cyst, surgically removed. His blood test were as follows: Sodium 125mmol/l, TSH 0.10mU/l, free T4 10.2pmol/l, freeT3 2.6pmol/l, cortisol < 28nmol/l, prolactin 240mU/l, FSH 1.8U/l, LH 0.3U/l. He was commenced on prednisolone 3mg and continued on levothyroxine 125mg. Initial CT Head showed suprasellar lesion with right sided mastoiditis. MRI pituitary showed a centrally cystic sellar and suprasellar lesion with peripheral enhancement, thickening of the pituitary stalk and abnormal signal in retro-chiasmatic tracts. Visual field (VF) assessment showed a left temporal superior visual field defect with normal right vision. The differential diagnosis was cystic macroadenoma, atypical hypophysitis or previous apoplexy. Pituitary MDT discussion advised to send off a vasculitis screen that showed weakly positive c-ANCA, PR3 antibody positive at 7.3 IU/ml (normal range upto 1.9). All other antibodies were negative including negative TB Elispot. A repeat VF assessment however, showed progression to bitemporal quadrantanopia. A diagnosis of ANCA-associated vasculitis was established and prednisolone was increased to 60 mg. A pituitary biopsy was considered if no improvement in visual fields. A repeat MRI after 6 weeks showed interval reduction in size with central cystic cavity collapsing down thus confirming likely an inflammatory process responding to glucocorticoid treatment. Once started on high-dose steroids, he reported polyuria and polydipsia with normal blood glucose levels. Awater deprivation test was consistent with a diagnosis of cranial diabetes insipidus which was managed with desmopressin. He was commenced on rituximab 1g, two weeks apart followed by a gradual reduction of prednisolone to meintenance dose of 3mg. Although he was eventually found to have hypogonadotrophic hypogonadism however wasn't started on testosterone replacement due to absence of any symptoms. Subsequently, he showed good clinical and radiological improvement and was able to return to work. On repeat MRI further reduction in size of pituitary gland was noted, normal thickness of stalk and uniform contrast enhancement. He remains under regular clinical follow up with a plan to continue 6-monthly rituximab infusions for remission maintenance and periodic pituitary MRI surveillance. This case posed a diagnostic challenge given the absence of many systemic features of vasculitis. In addition, it highlights the delayed diagnosis of posterior pituitary dysfunction which was unmasked by the high dose steroids. It also emphasizes the importance of the MDT approach to manage such cases.
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EP833

Case Series of Cranial Diabetes Insipidus secondary to Presumed Lymphocytic Hypophysitis Presenting During Pregnancy
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Introduction
We present two pregnant women who were referred to obstetric endocrinology service with polyuria and polydipsia. They were investigated and treated for diabetes insipidus (DI). In both cases, the underlying pathophysiology was ADH insufficiency secondary to autoimmune lymphocytic hypophysitis. There are currently no consensus guidelines on the diagnosis of DI during pregnancy. These cases highlight best practice and endorse MDT management of chronic hypopituitarism.
Cases
Patient 1 was referred at fifteen weeks gestation with excessive thirst and polydipsia. She had a background of autoimmune lymphocytic hypopysitis (aged 16) diagnosed after resection of a presumed pituitary macroadenoma. She had been well off endocrine replacement in the interim 14 years but remained amenorrhoeic (she declined HRT). She conceived with IVF and became symptomatic with D.I. at 5 weeks' gestation. She had a water deprivation test

during her pregnancy and outside of pregnancy, the result would have been normal. She was treated with dDAVP, stopping after delivery. Patient 2 was also referred at twenty weeks' gestation with thirst (drinking twenty litres/day) and nocturia. Her symptoms had started during a previous pregnancy two years previously, which ended in miscarriage. In her second pregnancy the symptoms became much worse. A random serum/ urine osmolality showed 310 mosmol/ kg and 37 mosmol/kg respectively. A non-contrast MRI showed symmetrical enlargement of the pituitary stalk, suggestive of autoimmune lymphocytic hypophysitis. She was treated with dDDAVP with prompt resolution of her symptoms and remains on treatment.
Discussion
Cranial DI is a state of increased thirst and water loss due to deficient ADH secretion. The diagnosis is complicated by physiological changes during pregnancy. Pregnancy is a state of fluid retention, mediated by changes in water homeostasis; pregnant women feel thirst at lower serum osmolarities and pass higher volumes of urine. Both of our patients had a primary deficiency of ADH to due lymphocytic hypophysitis. In one of the patients, the damage was subclinical and unmasked by pregnancy. In pregnancy the vasopressinase activity of placental cystine aminopeptidases leads to a 3-4 fold increase in ADH catabolism. Their pituitary glands were unable to meet this increased demand. Differential diagnosis is HELLP syndrome / liver impairment. This was ruled out in our patients. Our patients were treated successfully with desmopressin, which is safe in pregnancy and required regular monitoring for water intoxication and hyponatremia. dDAVP is more resistant to placental vasopressinases than endogenous ADH.

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EP834

The Role of Medical therapy and Radiotherapy in the management of Pituitary Macroprolactinomas

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Introduction

Background
Pituitary adenomas can be divided into functioning pituitary adenoma (FPA) and non-functioning pituitary adenoma (NFPA). Pituitary adenomas can also be classified based on their size as microadenoma(< 1cm) or macroadenoma (> 1cm).
Cases
1. A 33-year male was admitted with a 4-month history of headaches, generalized aches and pains, weight loss, lethargy, and erectile dysfunction. He was reviewed by the Endocrine team and his hormonal profile showed TSH 2.62, FT4 4.2, FT3 3.7, 9 am cortisol 37, Prolactin 12,000, LH 2.5, FSH 5.4, testosterone 1.7. IGF-1 was 211. He was started on Cabergoline and responded well with normalization of prolactin level to 217. His testosterone level improved alongside LH and FSH. He did not require surgical intervention or Radiotherapy 2. A 63-year-old man presented to Emergency with headaches and visual disturbance. He was reviewed by the neurology team and was found to have bi-temporal hemianopia. CT head revealed a pituitary mass. His past medical history includes erectile dysfunction, gynecomastia, and general lethargy. His blood test revealed a low testosterone level, low LH, and low FSH. Of note, his prolactin level was > 100,000. MRI pituitary revealed pituitary macroadenoma with suprasellar extension. He was started on cabergoline with some response and normalization of his visual field. His prolactin level initially dropped to < 500 however further rose to > 20,000 despite the dose escalation of cabergoline to 10mg weekly. MRI demonstrated significant tumour enlargement and an increase in size. He was treated with external beam radiotherapy, with a reduction in tumour size and an improvement of prolactin to around 3000. The patient was switched to the maintenance dose of quinagolide 300mg once a day and the prolactin level improved to < 3000.
Discussion
Most pituitary prolactinomas respond well to dopamine agonists as demonstrated by case 1. The remission rate with cabergoline or bromocriptine is about 70-90%(3,4). Radiotherapy should be considered for patients with pituitary macroprolactinoma which is unresponsive to medical therapy as demonstrated in case 2.
Conclusion
The 1st line of treatment for pituitary prolactinomas is a dopamine agonist(2,3,4). Radiotherapy should be considered in those patients not responding to medical therapy.

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EP835

Pituitary metastasis from colon cancer in a young patient

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Introduction
Pituitary metastases account for approximately 1% of pituitary lesions, most frequently originating from lung or breast cancer. We describe a case of a pituitary metastasis from colon cancer, a rare origin.
Case report
a 36 year-old male, previously healthy, came to the emergency department for new onset jaundice and fever. He also had headaches for the last 3 months, and for the last month diplopia, left palpebral ptosis and low libido. Physical examination confirmed jaundice (sclera and skin), low weight, abdominal pain at the right upper quadrant, left palpebral ptosis and right III and VI nerve paralysis. Abdominal-pelvic CT revealed hepatomegaly with several lesions (suggesting metastases), multiple mesenteral, lombo-aortic, pelvic and inguinal adenopathies and an infiltrative mass in the sigmoid colon. The remaining investigation confirmed the diagnosis of metastatic colon cancer with obstructive jaundice and cholangitis. Brain MRI showed an extensive, infiltrative sellar and clival mass, with suprasellar extension causing optic chiasm and hypothalamic compression, bilateral cavernous sinus invasion (knosp 4), sphenoid sinus invasion and bone erosion and extension to petrous bone apex with left Meckel cavum obliteration, suggestive of metastasis in this clinical picture. 18F-FDG PET-CT revealed high uptake by the sellar lesion (as well as for the primary tumor and remaining metastases). Pituitary function tests revealed pan-hypopituitarism and slight prolactin elevation. He was started on hydrocortisone and levothyroxine. A few days later, the patient complained of increased thirst and urinary output (polyuria confirmed by 24h urine collection), with dehydration at physical examination. Diabetes insipidus was confirmed, so desmopressin was started. The patient started complaining of decreased sensation in the left upper face and it was decided to do palliative radiation treatment (30Gy), that was ineffective for symptom control and he died shortly after the end of treatment, with progressing systemic disease. Overall, the patient survived for 2 months after diagnosis and never started systemic treatment for his cancer nor transsphenoidal surgery was considered because his physical condition never allowed to.
Conclusion
Although it was not confirmed histologically, aggressive characteristics in MRI, 18F-FDG uptake, diabetes insipidus and a confirmed metastatic colon cancer diagnosis, makes pituitary metastasis the most likely diagnosis. There are only a few cases of pituitary metastases from colon cancer described in literature, usually presenting with visual complaints, most of them treated surgically, with poor prognosis.

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EP836

Clinical profile of Acromegaly patients in a teritary endocrine center in Kathmandu, Nepal

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Nepal has limited data on acromegaly patients. We did a retrospective study of acromegaly patients who were diagnosed in our center or were referred to our center. We included 10 patients of acromegaly who presented in our center from January 2018 to December 2022. Four (40%) were males and six (60%) were females. Their mean age was 38.70 +/- 6.51 years, ranging from 31 to 50 years. The mean BMI was 26.13 +/-1.77 kg/m^2. The most common presenting symptom was joint pain (90%) followed by headache and peripheral neuropathy (40% each). Three patients (30%) patients had visual problems with visual defects. All patients had acral enlargement, prominent supraorbital ridge and prognathism. Increased sweating was seen in 3 patients (30%). Four (66.66%) out of six female patients had menstrual abnormalities; one forty-four years old patient had amenorrhea for two years and another female of thirty-one years of age had amenorrhea for eight months. Hypertension was seen in three (30%) patients and diabetes was seen in seven (70%) patients. One (10%) patient had hypothyroidism. All patients had elevated basal GH and IGF1. Mean basal GH was 48.78 +/- 43.67 ng/ml, ranging from 6.36 to 160 ng/ml with median of 44.29 ng/ml. Mean IGF-1 was 515.25 +- 316.03 ng/ml ranging from 117 to 954 ng/ml with median of 522.65 ng/ml. Hyperprolactinemia was seen in two (20%) patients while secondary hypogonadism was seen in one (10%) patient and secondary hypercortisolism was seen in one (10%) patient. One (10%) patient had pituitary microadenoma whereas nine (90%) patients had pituitary macroadenoma. Seven patients (70%) underwent surgery to remove pituitary adenoma and three patient (30%) refused surgery. Out of seven patients who had surgery, six patients (60%)

underwent endoscopic trans-sphenoidal surgery and one (10%) patient underwent transcranial pituitary adenectomy. Post operatively one patient (10%) developed diabetes insipidus, one (10%) patient developed third cranial nerve palsy and hypocortisolism. The mean GH of seven patients who underwent surgery was 10.22 +/- 7.73 ng/ml and IGF-1 was 398.90 +/-268.35 ng/ml ranging from 143 to 879 ng/ml. None of the patients had remission. Three (30%) patients received second line treatment. Among them two (20%) patients underwent radiotherapy; 1(10%) received EBRT (External beam radiation therapy) and 1(10%) underwent gamma knife surgery. One patient (10%) received Sandostatin (Octreotide LAR). One (10%) of our patient had to undergo resurgery- transphenoidal pituitary surgery.

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EP837

Hyperprolactinemia in a patient with the kidney failure: a rare case of macroprolactinoma and autosomal dominant polycystic kidney disease

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Introduction
Autosomal dominant polycystic kidney disease (ADPKD) is an inherited kidney disease characterized by the development and growth of cysts causing a progressive kidney enlargement and the end-stage renal disease (ESRD). The incidence of brain aneurysms in patients with ADPKD is high thus screening is recommended. The association of pituitary incidentalomas and ADPKD is rarely described in the literature. All reported pituitary adenomas in patients with ADPKD were functional growth hormone (GH) secreting adenomas. We represent a rare case of macroprolactinoma in a patient with ADPKD and ESRD.
Case presentation
A 43-year-old male with ADPKD and ESRD, treated with chronic haemodialysis, was referred to a Magnetic Resonance Imaging (MRI) of the head as a part of the pre-transplantation evaluation. The MRI scan showed the sella turcica filled with an enlarged pituitary gland protruding cranially into the suprasellar cistern, raising and shortening the infundibulum, and reaching the lower contour of the optic chiasm and nerves. The pituitary gland had total dimensions of 21 x 12 x 17 mm (CC x AP x LL). The patient was referred to an endocrinologist, and a laboratory examination was performed. The results were as follows: elevated prolactin level > 4255.3 mIU/l (n.r. 56.0 - 278.4), low FSH 0.88 IU/l (n.r. 1.27 - 19.26) with LH 4.99 IU/l (n.r. 1.24 - 8.62), total testosterone 8.22 nmol/l (n.r. 5.21 - 23.70), sex hormone binding globulin 26.8 nmol/l (n.r. 13.3 - 89.5) and free testosterone 185 pmol/l (n.r. 170 – 660). The function of thyrotropic, corticotropic and somatotropic cells was normal. The patient did not complain of mass effect symptoms, such as a headache or visual field disturbance, and his visual field examination was normal. He had no symptoms of hypogonadism and was a father of one child. A diagnosis of a prolactin-secreting pituitary macroadenoma (macroprolactinoma) was made and the bromocriptine therapy was started. After two months, the prolactin level was normalized (175.6 mIU/l; n.r. 56.0 - 278.4), together with the FSH level. The bromocriptine therapy was continued, while the check-up pituitary MRI is planned 6 months after the initiation of the therapy.
Conclusion
Hyperprolactinemia is a common endocrine abnormality in patients with the kidney failure, most often not requiring a specific treatment. This case report highlights that a patient with the kidney failure and extremely high prolactin levels, especially if accompanied with a headache or visual field disturbance, needs to be examined for a prolactinoma.

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EP838

A sheehan's syndrome revealed by cardiovascular collapse

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Introduction
Sheehan syndrome (SS), or postpartum pituitary necrosis, is a rare but potentially serious complication of postpartum. we describe a patient whose diagnosis of sheehan's syndrome was delayed and revealed by a cardiovascular collapse.
Case report
A 36 year old femele patient, admitted to the intensive care unit in a state of septic shock due to pyelonephritis, was intubated, ventilated and put on noradrenaline in SAP and antibiotic therapy, in view of the non-improvement and low blood pressure figures despite the filling and vasoactive drugs, as well as hypoglycemia with a hyponatremia of 110 and hyperkalemia of 6 on the ionogram, acute adrenal insufficiency was suspected and the 8-hour cortisol level confirmed the diagnosis (0.8 mg/dl), patient put on intravenous hydrocortisone hemisuccinate. The evolution was marked by an improvement, patient extubated and weaned from vasoactive drugs, the interrogation revealed an antecedent hemorrhagic childbirth with absence of milking and absence of return of childbirth, and the patient kept an important asthenia in postpartum but and consulted each time for a digestive picture made of abdominal pains and nausea put under symptomatic treatment without the diagnosis of adrenal insufficiency being suspected. The patient was then admitted to the endocrinology department for further management with evidence of a gonadotropic, corticotropic and thyrotropic deficit, the somatotropic axis was not explored, the pituitary MRI was without anomalies.
Discussion
This observation is typical of Sheehan's syndrome, both in its clinical presentation and in the diagnostic errors that it can cause.
Conclusion
Postpartum pituitary necrosis is a difficult diagnosis in the acute phase and is often overlooked. This diagnosis should be evoked in any patient who has had a collapse during childbirth, whatever its cause, in front of the appearance of early headaches or a meningeal syndrome, and/or in front of the later appearance of the classic signs of pituitary insufficiency (absence of lactation, weight loss, asthenia, arterial hypotension, secondary amenorrhea)

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EP839

Adipsic Diabetes Insipidus After Transsphenoidal Surgery for Supra-sellar Intraventricular

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Presented case demonstrates a rare diencephalic pathology — adipsic diabetes insipidus (ADI) with severe hypernatremia in a 58-year-old woman after ttranssphenoidal removal of stalk intraventricular craniopharyngioma. ADI was diagnosed because of hypernatremia (150–155 mmol/l), polyuria (up to 4 liters per day) and absence of thirst. Normalization of wa- ter-electrolyte balance occurred on the background of desmopressin therapy and sufficient hydration in postoperative pe- riod. After release from the hospital, the patient independently stopped desmopressin therapy and did not consume an adequate amount of fluid of the background of polyuria. This led to severe hypernatremia (155–160 mmol/l) and rough mental disorders. Patients with ADI need closely monitoring of medical condition and water-electrolyte parameters, appointment of fixed doses of desmopressin and adequate hydration.

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EP840

Severe hyponatremia in hospitalized patient caused by hypopituitarism due to empty sella

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Background
Hyponatremia is the most common electrolyte disorder in clinical practice, whereas severe hyponatremia can be life-threatening if not diagnosed and managed appropriately. Severe hyponatremia can be the only presentation of several endocrine and non-endocrine diseases, and investigation for underlying causes and its appropriate management can be potentially life-saving. Severe hyponatremia is frequently overlooked as the presenting manifestation hypopituitarism. Herein, we describe a case of delayed diagnosis of hypopituitarism due to empty sella.
Case report
A 61-year-old patient was treated in a hospital for pneumonia, hyponatremia, when he developed seizure and coma. After two weeks of treatment, the patient was discharged, but on the next day his condition worsened with fatigue, dizziness, nausea, progressive somnolence, and was re-hospitalized in our emergency department. Upon admission, BMI = 16.3 kg/m^2, BP = 125/80 mm/Hg, HR = 79, RR = 19. Laboratory tests revealed severe hyponatremia (Na = 109 mmol/l), with normal potassium and glucose levels. IV infusion of 3.0%NaCL was initiated instantly with increase in sodium levels ≈6 mmol/l per 24h in order to avoid further neurological complications. Further tests:

serum osmolality 227 mOsm/kg, urine osmolality 493 mOsm/kg H<inf>2</info>O, urine sodium 118 mmol/l, serum cortisol 1.62 µg/dl (5,27-22.45), ACTH 12.10 pg/mL (0.1–46.0), FT4 0.43 ng/dl (0.89–1.76), FT3 0.9 pg/ml (3.1-6.8), TSH 1.91 µIU/mL (0.35–5.5). Other investigations unremarkable. He had been diagnosed with hypothyroidism (unknown etiology) 40 years ago, and was on levothyroxine 50 µg since then. According to the clinical and laboratory findings, he was diagnosed with hypopituitarism—secondary adrenal insufficiency, central hypothyroidism. Pituitary MRI revealed empty sella syndrome. Patient was started on IV hydrocortisone instantly and levothyroxine dose was increased in a few days. After hydrocortisone initiation, patient's symptoms resolved with complete biochemical and clinical improvement. He was discharged on 20 mg hydrocortisone and 100 µg levothyroxine daily without any worsening during follow-up visits.

Conclusion

Our case demonstrates the importance of management of severe hyponatremia along with comprehensive workup to establish the cause of hyponatremia and appropriate management. Adequate treatment of hyponatremia in our patient led to a complete recovery without consequences.

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EP841

Sheehan's syndrome presenting as post-partum depression : a case report

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Introduction

Sheehan's syndrome or Simmond's disease is a partial or complete postpartum hypopituitarism caused by pituitary infraction and necrosis that usually occurs as a complication of massive postpartum hemorrhage or severe hypotension during or after labor and delivery. We present the case of Sheehan's syndrome presenting postpartum depression.

Case

A 40 years old woman, referred to our department by her psychiatrist for exploration of central hypothyroidism. Her medical history is marked by the occurrence of postpartum depression one month after delivery for which she was put under antidepressant and anxiolytic for about 4 months. Her last pregnancy, the childbirth was a full-term vaginal delivery at home which was complicated with profuse bleeding that required transfusion. The evolution was marked by the inability to lactate her child and the cessation of her menstrual cycles after the delivery. The physical examination at the time of admission revealed an ill-looking patient, bradyphrenia, asthenia, cold extremities, pallor, pronounced wrinkles, rarefaction of body hair and atrophied breasts The biological assessment showed a corticotropic insufficiency with a 8 am cortisol of 26ng/ml, a thyrotropic insufficiency of central origin with FT4 below 1pmol/l and a hormonal profile of hypogonadotropic hypogonadism The hypothalamic-pituitary MRI was requested and came back in favor of an intrasellar arachnoidocele. The patient was put on hydrocortisone, levothyroxine. The evolution was marked by the improvement of her well-being. One month later, she was started on oestrogen and progesterone hormonal therapy.

Discussion & Conclusion

The psychiatric features of hypopituitarism can be attributed to a combination of hypothyroidism, hypoglycemia and hypocortisolism, and have been shown to spontaneously resolve under adequate hormone replacement. In fact, medical and obstetric history, and physical examination are of paramount importance in the diagnosis as most patients will consult for nonspecific symptoms which cause delays in management.

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EP842

Spontaneous involution of a cystic pituitary adenoma

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Pituitary adenomas (PAs) account for 15-20% of intracranial tumors. PA with a cystic component are characterized in the MRI by a sellar, symmetrical, round or ovoid mass that enhances on T1- or T2-weighted images but does not concentrate gadolinium. We present the case of a 48-year-old man who in a headache study by Neurology requested a CT scan showing a cystic pituitary macroadenoma of 1.25cm confirmed by pituitary MRI. In the initial analysis, the pituitary function was preserved, but in the follow-up he was diagnosed with central hypothyroidism and hypogonadotrophic hypogonadism, so replacement treatment was started. In addition, a visual field study was performed, being normal. As it was a clinically non-functioning asymptomatic pituitary adenoma, we opted for conservative follow-up without surgery. During the follow-up of the patient, a control pituitary MRI requested three years later revealed a significant decrease in the size of the pituitary lesion with cystic semiology, with dimensions of 8x3mm. This decrease in size was confirmed in subsequent imaging tests, although the hormone deficits presented by the patient persisted. Nonfunctioning PAs can go unnoticed for years, and be diagnosed incidentally or when they grow and produce compressive symptoms (headaches, visual impairment) or hormonal deficiencies. In patients with asymptomatic, clinically nonfunctioning pituitary incidentalomas it is recommend conservative follow-up without surgery, with periodics MRI. Macroadenomas have a propensity to grow, but it has been seen that a small percentage (approximately 10%) may undergo spontaneous volume regression, perhaps due to silent ischemia, so continuous follow-up with repeated imaging is justified. Periodic reassessment of pituitary function is recommended in patients with macroincidentalomas because they are at risk of developing hypopituitarism. Medical therapy of pituitary incidentalomas has not been systematically studied. The reported efficacy of do pamine agonist, somatostatin analogues, and GnRH analogues varies widely. In the present case, there was a significant decrease in the size of the PA during follow-up without surgical or medical treatment, hence the importance of periodic radiological follow-up. In some cases, when tumor size regression occurs, pituitary function can be restored, a fact that did not occur in our case, so we will continue with clinical, radiological and biochemical follow-up of the patient.

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EP843

Acromegaly: predictive factors for long-term remission

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Introduction

The management of acromegaly is commonly based on selective transsphenoidal adenomectomy (STA) as a first-line treatment, and other therapeutic options including somatostatin analogues (SA), dopamine agonists (DA) and radiotherapy as second-line treatment or in case of operative contraindications. The aim of our study was to assess the remission rate and to determine the predictive factors for long-term remission in acromegalic patients.

Methods

We conducted a retrospective study including 27 acromegalic patients followed in the endocrinology department of Charles Nicolle hospital during the period from 1989 to 2022. Clinical, biochemical, imaging and therapeutic data were extracted from medical records. According to hormonal outcome, patients were subdivided into two groups: remission vs improvement/stabilization.

Results

There were 16 (59%) women and 11 (41%) men with a mean age at the diagnosis of acromegaly of 46.6 $\pm$ 13.7 years. The median (IQR) initial GH level was 21.6 ng/ml (7.8-47.0). STA, SA, DA and radiotherapy were used in 67, 22, 4 and 26% of cases, respectively. Long-term remission was obtained in 10 patients (37%), while most patients (63%) had a persistent disease (improvement or stabilization). Patients who underwent STA had a significantly higher remission rate compared with unoperated patients ($P = 0.009$). We did not found significant correlations between adenoma size, initial GH and post-therapeutic GH levels. We did not observe significant associations between remission rate and the following parameters: age, sex, locoregional invasion, pituitary deficiencies, vision loss, use of SA, DA and radiotherapy.

Conclusion

The prognosis of acromegaly depends mainly on early and effective tanssphenoidal resection of somatotroph adenoma. Medical treatment and radiotherapy can not lead to remission unless combined with STA.

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EP844

A case report of pituitary macroadenoma presenting with visual disturbance due to suspected cataract

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Introduction
Pituitary adenomas are benign tumours of the pituitary gland with an estimated prevalence rate of approximately 17%. Around 1 in 600 people have macroadenoma (>1cm) that can present with variety of visual problems classically as bitemporal hemianopia due to compression of the optic chiasm.
Case presentation
50-year-old male was admitted with 3months history of worsening headache and 4months of visual disturbances. Initially he was seen in an eye clinic and diagnosed with cataract however, on the day of his cataract operation was told he does not have cataract and was sent for further investigations. In the past 4weeks his headaches had escalated to 10/10 pain severity scale that was not relieved by analgesia and his vision was getting worse. He reports of change in shoe size and his ring no longer fitting. He complained of increased frequency of urination, snoring at night-time and intermittent sweating. On examination he was found to have bitemporal hemianopia more severe on the right inferior quadrants, reduced nasal field on the right eye but rest of the cranial nerves were intact. His lower jaw was producing but no evidence of overbite or large hands. Nil significant past medical history.
Investigations
MRI pituitary showed large pituitary lesion measuring 4.8x1.7x2.9 cm extending into suprasellar cistern and compressing the optic chiasm and the hypothalamus and part of the floor of the third ventricle. The lesion is extending downward into the sphenoid sinus.
High prolactin 12788
Low cortisol level of 34
Low T4 (3.4) and T3 (2.8) (TSH normal)
Low FSH (0.9) and LH (<0.3)
Low testosterone(<0.1)
Low IGF-1 (60)
Management
Referred to the neuro-pituitary MDT. Commenced on cabergoline and prolactin decreased from 12788 to 2846 after one week Also started on hydrocortisone 10mg twice daily and levothyroxine 50micrograms daily. Endoscopic transsphenoidal surgery for pituitary lesion was carried out.
Discussion
Visual disturbances in particular bitemporal hemianopia is a common clinical presentation in pituitary macroadenomas however, in this case the patient initially presented at an Eye Clinic hospital and was diagnosed as cataract which is not common. Pituitary macroadenoma in particularly prolactinomas can be managed conservatively with dopamine agonist such as cabergoline however, in certain cases such as patients with resistant or intolerance to domine agonist, or worsening vison an endoscopic transsphenoidal surgery may be offered.
Conclusion
It is important to consider cranial or pituitary issues as differentials when seeing patients complaining with headache and visual changes.

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EP845

Retrospective Evaluation of Pituitary Adenomas from clinical, laboratory and medical aspects

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Pituitary adenomas arise from adenohypophyseal cells and progress with increased comorbidity and mortality. It is important to examine the diagnosis, prevalence, course and treatment of the subgroups of the disease in our country because pituitary adenomas are seen in the most productive periods of life and have important clinical results. In our study, 667 pituitary adenoma patients who applied to Eskişehir Osmangazi University Medical Faculty Hospital Endocrinology Department between 1980-2018 were evaluated retrospectively and observationally. The information of the patients was scanned from the hospital information management system and outpatient clinic patient files. Scanned information; age, gender, age of diagnosis, follow-up year, application complaint, size, location, hormone levels at the time of diagnosis and after treatment, type of medical treatment used, number and type of operation of pituitary adenoma, before medical or surgical treatment and post-adenoma size and if any, residual/recurrent pituitary adenoma size, chiasma compression, postoperative hormone activity, history of RT for adenoma. 171 (25.6%) were nonfunctional adenomas, 356 (53.4%) were prolactinomas, 121 (18.1%) were acromegaly, 16 (2.4%) were Cushing disease and 3 (0.4%) were TSHoma. 340 (51.1%) microadenomas, 195 (29.1%) macroadenomas, 132 (19.8%) invasive macroadenomas were detected. It should be kept in mind that delay in diagnosis will cause important problems such as decrease in quality of life, disability, preparing the ground for additional diseases, and showing a mortal course. As a result, the information obtained from the careful examination and the request for the relevant laboratory and radiological tests will lead us to early diagnosis.

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EP846

Cyclic cushing syndrome: a case report

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Introduction
Intermittent Cushing's syndrome is characterized by alternating episodes of hypercorticism with periods of eucorticism. It is a rare but well-defined entity and should be known. It remains a diagnostic challenge sometimes particularly difficult in endocrinology, we report a case.
Case presentation
A 22-year-old diabetic patient on metformin, who consulted us because of a weight gain with the appearance of stretch marks for 2 months. The clinical examination revealed severe obesity with TTP, aconthosis nigricans, complete and flagrant clinical cushing syndrome. At this time, we could not explore the patient hormonally. The hypothalamic-pituitary MRI showed a pituitary microadenoma measuring 3.3*2.4mm. The workup for cushing's syndrome was unremarkable except for diabetes with a HBa1C of 7%. After 5 months, the patient had regression of stretch marks with a significant weight loss of 9kg, and hypoglycemic malaise motivating the discontinuation of diabetes treatment. The diagnostic workup for cushing's syndrome, including urine cortisol levels and a 1mg overnight dexamethasone suppression test, was normal. The diagnosis of cushing's disease with cyclic hypercorticism was considered. The management consisted of a quarterly clinical and biological evaluation
Discussion
The diagnostic criteria for intermittent cushing's syndrome include three episodes of hypercorticism and two episodes of eucorticism, although these criteria are valid for most patients, they can be difficult to achieve especially if the intercycle phase is large. Our patient presented with a clinically diagnosed episode of hypercorticism followed by an episode of spontaneous eucorticism. The fluctuating clinical presentation and discordant biochemical findings make this intermittent Cushing syndrome extremely difficult to diagnosis. Frequent measurements of urinary cortisol or better salivary cortisol level are reliable and practical diagnostic tools, and should be repeated, especially when clinical signs and symptoms reappear.
Conclusion
This observation illustrates the diagnostic challenge of intermittent Cushing's syndrome, so clinicians should be aware that hypercorticism may occur periodically and actively search for it in all patients with suspected Cushing's syndrome.

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EP847

Outcome of Bilateral Adrenalectomy in Cushing's Syndrome

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Introduction
Cushing disease is the most common cause of endogenous hypercortisolism. Pituitary surgery is the first-line treatment and bilateral adrenalectomy is the option of last resort due to its severe consequences.
Observation
This is a 24-year-old patient followed for cushing disease revealed by a severe cushing syndrome, a urinary cortisol at 20 times normal and negative dexamethasone suppression test with a pituitary microadenoma on MRI. He was operated with an anatomopathological result of an acidophilic pituitary adenoma expressing anti prolactin and anti ACTH antibodies with a proliferation index (KI 61) at 1%. The exploration in post-pituitary surgery revealed the persistence of the severe Cushing's syndrome with discovery of a right adrenal

mass in favor of an adenoma. The patient underwent bilateral laparoscopic adrenalectomy with no histological evidence of malignancy. He was put on replacement therapy. The symptoms of hypercortisolism improved (weight, hypertension, diabetes, depression).
Discussion
Cushing disease is responsible for severe morbidity and its management is a therapeutic challenge. Bilateral adrenalectomy was chosen as the last resort in our case, given the severity of symptomatology. Monitoring by adrenocorticotropic hormone and pituitary MRI is necessary because of the risk of developing Nelson's syndrome.
Key-Words : Hypercortisolism-Cushing disease -treatment-adrenalectomy
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EP848

Opposite tumoral and hormonal responses to low-dose pasireotide in Cushing's Disease
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Pasireotide (Pas) is a multireceptor-targeted somatostatin analogue approved for the treatment of patients with Cushing's Disease (CD) who fail or are poor candidates to surgery. Pas markedly improves signs and symptoms of the disease, reduces urinary free cortisol (UFC) up to its normalization in 55% of patients and pituitary tumour size in up to 100%. Here we present a patient with severe recurrent CD treated with Pas and showing opposite results between hormonal levels and pituitary tumour size. A 54-year-old woman was diagnosed with CD in 2008. A right 8 mm intrasellar adenoma was totally removed by TNS. After seven years the disease recurred (UFC 4x Upper Limit of Normal Range (ULNR), ACTH 60 pg/ml, reference range 9-52) and MRI showed an intrasellar right adenoma tightly close to cavernous sinus (CS). She underwent a second TNS surgery, but, in spite of an apparent total removal of the adenoma, hypercortisolism worsened (UFC 40x ULNR, ACTH 237 pg/ml). MRI showed a tiny remnant of the adenoma adjacent to CS and ketoconazole (Kcz) was started at 800 mg/daily dose. Due to the persistence of pathological UFC levels, sc 600 μg bid Pas was added. The combination therapy firstly induced UFC and ACTH normalization (0.8x ULNR, 33 pg/ml, respectively) and later on hypoadrenalism, so that Kcz was withdrawn and Pas maintained, due to its higher efficacy and aiming to control the size of the adenoma remnant. Pas obtained a marked clinical improvement, diabetes mellitus occurred requiring metformin and dulaglutide. Three months after Pas starting the pituitary MRI showed a slight tumor shrinkage. Due to the occurrence of hypoadrenalism, a steroid replacement therapy was started. Adrenal insufficiency persisted notwithstanding the orogressive tapering of Pas dose to 150 mg once daily. Pituitary MRI performed at 12 and 24 mos during low (150 mg once daily) Pas dose showed a few millimeters increase of the remnant, whereas ACTH levels remained normal (31 pg/ml). Diabetes mellitus remitted, requiring only dietotherapy. This report suggests that in CD Pas induces an opposite effect between hormonal profile and the increase of pituitary tumor size. This peculiar phenomenon might be a consequence of unusual low doses of Pas needed to control hormonal hypersecretion
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EP849

Ophthalmological complications in acromegaly: prevalence and associated factors
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Introduction
Somatotropin macroadenomas are associated with a considerable risk of ophthalmological impairment. The aim of our study was to determine the prevalence of ophthalmological complications and their associated factors in patients with acromegaly.
Methods
We conducted a retrospective study including 28 patients with somatotropin adenomas and followed in the endocrinology department of Charles Nicolle Hospital. Clinical, biochemical and imaging data were collected. Ophthalmological findings (visual acuity, visual field and fundus) were also recorded.
Results
There were 17 women and 11 men. The mean age at the diagnosis of acromegaly was 45.9 $\pm$ 13.9 years. Ophthalmological examination showed reduced visual acuity (RVA), visual field defects and papilledema in 25, 36 and 22% of cases, respectively. GH nadir during oral glucose tolerance test ($P<$ 10-3) and the tumor size ($P=0.001$) were significantly higher in patients with suffering from RVA. ACTH and cortisol levels were on the contrary lower among these patients ($P=0.001$). Aggressive tumors ($P=0.038$), optic chiasm invasion ($P<$ 10-3) and corticotroph deficiency ($P=0.022$) were associated to an increased risk of vision loss. Visual acuity was negatively correlated with tumor size ($r=$-0.727; $P<$ 10-3) and the number of pituitary deficiencies ($r=$-0.621; $P=0.005$). However, age, sex, cavernous or sphenoidal sinus invasion did not have a significant association with RVA.
Conclusion
Optic pathway compression, caused by somatotropin macroadenomas exposes to a considerable risk of vision loss. Tumor size, aggressive tumors, optic chiasm invasion, GH nadir level and the number of pituitary deficiencies help to predict that risk.
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EP850

Intrasellar arachnoid cysts – a benign entity with significant clinical impact: report of two cases
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Introduction
Intrasellar arachnoid cysts are rare and clinically resemble nonfunctional pituitary adenomas. Arachnoid cysts should be considered in the differential diagnosis of cysts developing in the sellar region, together with cystic pituitary adenoma, craniopharyngioma, epidermoid cysts, and Rathke's cleft cysts. Symptomatic cysts are operated but can recurr.
Case presentation
We present 2 cases of compressive intrasellar arachnoid cysts occurring in elderly patients who presented with severe loss of vision.
Case 1
A 75-year-old woman presented with bitemporal hemianopsia and recurrent falls without loss of consciousness. Cerebral MRI showed a sellar and suprasellar cystic lesion measuring 25/23/20mm, compressing the pituitary gland and the optic chiasm. Endocrine assessment was not performed. The patient underwent cyst resection and fenestration by transcranial microsurgery, with marked improvement of vision and visual fields. Pathology confirmed an arachnoid cyst. 9 months post-surgery, vision and visual fields deteriorated and a cyst recurrence was diagnosed on MRI. Repeat surgery resulted in visual improvement. The patient presented in our service 8 months after the second surgery with dizziness and severe asthenia. Hormonal tests revealed p nhypopituitarism and disconnection hyperprolactinemia (56.25 ng/mL). Hydrocortisone and L-thyroxine replacement were given. Visual fields were again affected, but subjective vision was good and the patient active and independent and the pituitary MDT recommended active monitoring of visual function and MRI.
Case 2
An 85-year-old woman with a history of tachycardia-bradicardia syndrome, an implanted pacemaker, aortic stenosis and heart failure, presented with long-standing (2 yrs) severe visual impairment "I see only half of people" and physical asthenia. Computerized visual field testing revealed findings atypical for the optic chiasm compression: right eye temporal hemianopsia and superior nasal quadrantanopsia and left eye paracentral visual field defect with superior nasal quadrantanopsia. A pituitary CT scan showed an enlarged sella turcica with fluid density, compressing the pituitary gland and optic chiasm. Laboratory tests demonstrated gonadotroph insufficiency and moderate hyperprolactinemia, without corticotroph and thyrotroph insufficiency. The patient and her family were against surgery. Pituitary MDT recommended close monitoring. We are trying to arrange an MRI scan, taking the pacemaker into account.
Conclusion
Intrasellar arachnoid cysts can affect pituitary function and visual function, requiring surgery. We describe two severely symptomatic cases, one with recurrence following repeat surgery and one with a patient refusal of surgery. Pituitary function should be assessed by hormonal tests pre- and post-operatively and replacement should be prescribed as needed.
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EP851

Echocardiographic features in patients with prolactinoma long-term treated with dopamine agonists

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Background

Dopamine agonists (DAs) were associated with valvular dysfunction in patients with Parkinson's disease due to their fibrotic effect through the serotoninergic receptor. It is more difficult to prove the same effects in patients with prolactinoma due to the lower doses, variable doses and the longer follow-up period.

Aim

To assess echocardiographic features in patients with prolactinoma under DA treatment.

Methods

Files of 91 patients diagnosed with prolactinoma were retrospectively assessed; 27 patients had at least one transthoracic echocardiographic (TTE) evaluation and were included in the analysis – 19 men and 8 women, median age at diagnosis 35 years-old (16-76), followed-up for a median of 5.4 years (0.2-18.4), macroadenomas prevailed (26 of 27 adenomas); median prolactin at diagnosis was 1363.7 ng/mL (75.5-30554). All subjects were treated with DAs – 25 with cabergoline (CAB) only, 1 with bromocriptine (BRC) only and one with both, consecutively. Median maximum CAB dose was 3.25 mg/week (0.5-14) with a median cumulative dose of 842.4 mg*year. Excepting 5 subjects, the rest were cured/controlled. Prolactin was measured by chemiluminescence.

Results

TTE was performed in only 29.7% of patients, despite high doses, long-term duration of DA treatment and presence of cardiovascular risk factors. All 27 patients had at least one classic cardiovascular risk factor (CVRF) – male gender (70%), age >55 years in men and >65 years in women (26%), smoking (19%), obesity (44%), dyslipidemia (78%), arterial hypertension (33%), diabetes mellitus (4%) and chronic kidney disease (33%). In average, the subjects had 3 CVRF Sixteen (60%) of patients had abnormal TTE during follow-up: 33% left ventricular hypertrophy (LVH), 40.7% had at least one grade I-II/IV valvular regurgitation (25.9% mitral and tricuspid and/or aortic, 11.1% isolated mitral, 3.7% isolated tricuspid); left ventricular function was normal in all patients but one, who showed mildly reduced left ventricular ejection fraction; 7 patients showed diastolic dysfunction. Maximum CAB dose $>$ 2 mg/week was associated with mitral regurgitation ($P < 0.05$). No patient required withdrawal of DA due to valve involvement. Study limitations include the small number of patients and non-standardized TTE evaluation.

Conclusion

TTE is still underperformed in long-term DA treated prolactinoma patients. Although atrio-ventricular regurgitation (mitral, tricuspid or both) was more frequent in our series than that reported in the general population, regurgitations were mild and clinically nonsignificant. Due to high prevalence of associated cardiovascular risk factors, lifestyle changes should become part of prolactinomas' approach.

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EP852

Three spontaneous pregnancies on active acromegaly, possible event !

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Pregnancies in women with acromegaly are rare. Data from the literature report the absence of fetal malformation, a rarely symptomatic increase in adenomatous volume, a possible risk of gestational diabetes and gravidic hypertension in women not controlled before pregnancy. We report the case of a 32-year-old woman, nulliparous, who consults for spaniomenorrhea associated with chronic headaches, in whom the diagnosis of acromegaly was suspected in the face of a very discreet acquired dysmorphic syndrome. Endogenous hypersomatotropism that cannot be curbed by OGTT was confirmed, with the presence of a pituitary macro-adenoma measuring 12 mm long on the hypothalamic-pituitary MRI. Surgical management was referred to the discovery of an evolving pregnancy of 08 weeks of amenorrhea (SA). The pregnancy was carried to term without incident. The morphological reassessment made at three months post-partum objectified an increase in the volume of the adenoma with an extension to the right cavernous sinus, consequently adenomectomy by trans-sphenoidal way was carried out, with the persistence of a tumoral residue. A few months later, in the face of the non-taking of contraception and despite the non-control of the disease by medical treatment, a second spontaneous pregnancy was diagnosed, carried to term without incident except for headaches and vesicular lithiasis diagnosed in the second trimester. The patient underwent a cholecystectomy two months after delivery. A third spontaneous pregnancy was discovered one month later despite hypersomatotropism. The occurrence of pregnancy during acromegaly is a rare situation. The risk of increased tumor volume, pregnancy-induced hypertension and gestational diabetes are reported, however close monitoring of these patients is required.

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EP853

Aggressive Cushing's: A Rare Case of Pancreatic ACTHoma in a Young Female

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Introduction

Adrenocorticotropic hormone-producing pancreatic neuroendocrine neoplasm is a rare type of pancreatic neuroendocrine tumor that causes ectopic adrenocorticotropic hormone syndrome. Cushingoid manifestations and metabolic abnormalities can occur rapidly. High index of suspicion is required for early diagnosis.

Case

A 31-year-old Filipino female presented with facial and ankle swelling that occurred 6 weeks before the visit. She also had acne, easy bruising, amenorrhea and frequent mood swings. There was reported weight gain of 3 kg a month prior. She had no known comorbidity, and had no unusual family history. At the time of admission, blood pressure of 130/80mmHg, pulse of 92/min, respiratory rate 20/min and temperature of 37.2C. Her BMI was 28kg/m2. She had muscle atrophy of the upper and lower extremities, facial flushing, posterior cervical fat pad, abdominal violaceous striae, and skin pigmentation. Her external genitalia was normal, Tanner Stage 5 consistent with adult pattern. Neurologic exam was unremarkable. She was examined for Cushing's syndrome. On initial tests, glucose was 406 mg/dl, HbA1C 10.7%, TSH 0.122 (NV: 0.55-4.78), Free T3 0.77 (NV: 2.3-4.2), Free T4 0.58 (NV: 0.89-1.76). Creatinine was 0.86 mg/dl, sodium was 140 mEq/l, potassium was 2.1 mEq/l showing hypokalemia. There was leukocytosis on her blood count, white blood cells 15,310/mm3 (neutrophils 94%, lymphocytes 3%). In the low-dose dexamethasone suppression test (DST), the serum cortisol concentration was 991.03nmol/l. Her adrenocorticotrophic hormone (ACTH) level was elevated at 577pg/mL. After high-dose DST, the serum cortisol concentration was $>$ 1750 nmol/l. No tumor was observed on pituitary magnetic resonance imaging. On abdominal computed tomography (CT) , a large, lobulated, heterogeneously-enhancing mass arising from the pancreatic body and tail measuring 7.5cm x 10cm x 10.9cm was seen. The mass had infiltrated the gastric fundus, and encased the splenic artery. Multiple non-calcified subcentimeter pulmonary nodules were observed on chest CT. CT-guided biopsy of the pancreatic mass was done. On microscopic examination, numerous atypical cells arranged with small clusters and sheets and scattered singly were found in the tumor. The cells had small to enlarged, hyperchromatic, ovoid to round nuclei and scant to ample delicate cytoplasm. On immunohistochemical staining, the tumor cells were stained positive for synaptophysin and chromogranin A, which are both neuroendocrine markers, as well as ACTH. However, the patient died prior to any definitive management.

Conclusion

ACTHoma is a very rare disease that causes hypercortisolemia. Reporting of similar cases will provide insight into its clinical features, immunohistochemical characteristics, diagnosis, therapy, and prognosis.

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EP854

Abstract withdrawn

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EP855

Risk of neoplasms in acromegaly : a monocentric retrospective study

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Background and aim
Acromegaly is a rare condition caused by an excessive secretion of growth hormone (GH) and insulin-like growth factor1 (IGF-1), which are responsible for exaggerated somatic growth, cardiometabolic disturbances and an increased neoplastic risk. This study aims to assess the tumorigenic potential of GH excessive secretion.
Patients and Methods
We conducted a retrospective study (1997-2020) at the Endocrinology department of Hedi Chaker University Hospital, Sfax, Tunisia. We involved 30 patients diagnosed with acromegaly, whose clinical, biochemical, and imaging peculiarities were collected from medical charts. Our patients benefited from a targeted screening for the more frequent neoplasia.
Results
Patients had a mean age of 45.8 ± 12.4 years with a male predominance (51.7%). Symptoms had been evolving for 5.1 ± 5.4 years. Acromegaly was secondary to a somatotropic adenoma in 96.7% and to a Growth hormone–releasing hormone (GHRH)-secreting pancreatic tumor in 3.3%. Clinical screening for breast cancer (breast palpation) and prostate cancer (digital rectal examination) did not reveal any suspicious lesions. Abdominal ultrasound showed one or more organomegalia in 33.3%: splenomegaly (16.7%), hepatomegaly (16.7%) and nephromegaly (8.3%). Colonoscopy performed in 14 patients was normal in 8 cases and showed polyps in 6 cases. Biopsy of the polyps did not reveal any signs of malignancy. Cervical ultrasound revealed a multi-nodular goiter in 16.7% and thyroid nodules in 11.1% of cases. Cytological study of suspected nodules confirmed their benign character.
Discussion
Despite remarkable therapeutic advances, 15-24% of deaths in acromegaly are due to cancer. The most reported neoplasia are gastrointestinal, thyroid, lung, breast and prostate. It is suggested that uncontrolled hypersecretion of GH/IGF-1 may promote the growth of tumor lesions, the carcinogenesis of pre-neoplastic lesions or the recurrence of previously treated cancers. Some studies also implicate genetic and epigenetic proto-oncogenes specific to acromegaly.

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EP856

Carcinoid Syndrome With Mesenteric Ischemia

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Introduction
Carcinoid tumors are included in the neuroendocrine tumor family. They are usually seen in the gastrointestinal tract and are asymptomatic unless liver metastases are present.
Case Report
A 44-year-old male patient was admitted with chronic crampy abdominal pain, diarrhea, and redness of the face and neck. He was admitted to the emergency department for abdominal pain many times before and was hospitalized in the general surgery department with the diagnosis of ileus. Abdominal CT and MRI enteroclysis were performed, metastases in the liver, increased wall thickness in the intestinal loops in the inferior of the umbilicus, and dilatation compatible with the intraperitoneal adenopathies and proximal ileus were observed. Biopsy taken from the mass in the liver was reported as neuroendocrine metastasis. In the patient who was found to have 25-fold higher 5-HIAA levels in the urine for 24 hours, systemic octreotide LAR 30 mg was started, considering carcinoid syndrome. Gallium 68 PET-CT was performed and Intense increased activity uptake in the small intestine segment at the level of the umbilicus was evaluated in favor of a possible primary focus. Multiple metastases in the liver and one metastasis in the sacrum were detected. After the first dose of octreotide treatment, the complaints of redness partially regressed, but the abdominal pain continued and gradually increased. Oral intake was stopped, but the patient whose abdominal pain did not regress was taken to an emergency operation. Widespread implants were seen in the peritoneum and omentum during A mass causing shrinkage in the small intestine mesos at 150 cm from the ligament of Treitz. It was observed that blood supply was impaired in the intestinal loops up to the middle part of the ascending colon. Necrosed areas were excised. After the operation, the complaint of pain regressed, and he was discharged with enteral nutrition solution supplementation.
Conclusion
It was thought that the patient developed mesenteric ischemia, possibly secondary to the substances released, or with a fibrotic structure that may occur in the mesentery. Although abdominal pain and diarrhea are seen in carcinoid syndrome, other causes of abdominal pain should also be reviewed.

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EP857

Controlling intracellular cortisol: Can HSD-1 inhibition reduce Cushing's syndrome morbidity and minimize adrenal insufficiency risk?

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Endocrinologists focus on circulating and excreted cortisol for diagnosis of, and to assess severity and treatment response in, Cushing's syndrome (Cs). However, in Cs, morbidity is mediated by excess cortisol binding to intracellular glucocorticoid (GC), mineralocorticoid (MC), and non-genomic receptors. We and others have demonstrated that 11b-hydroxysteroid dehydrogenase type 1 (HSD-1) is the source of about half of intrahepatocellular cortisol in healthy adults, patients with diabetes, and patients with mild hypercortisolism. The circulating concentration of cortisol is higher than cortisone, yet its bioavailability is limited, due to the former's greater affinity to plasma proteins. Free circulating cortisol and cortisone concentrations are similar, the latter providing a reservoir of "inactive" GC that enters cells and is rapidly converted by HSD-1 to cortisol. Patients with severe hypercortisolism who are deficient in HSD-1 activity showed no cortisol-related morbidity. A HSD-1 inhibitor prevented the deleterious effects of prednisolone on glycemic control and osteocalcin in a Phase 1 clinical trial. Mice without the *Hsd11b1* gene (which encodes HSD-1) or treated with a HSD-1 inhibitor were protected from glucose intolerance, hyperinsulinemia, hepatic steatosis, adiposity, hypertension, myopathy, dermal atrophy, and trabecular bone loss associated with GC administration. In states of glucocorticoid excess, liver HSD-1 activity is enhanced, as assessed by the HSD-1 ratio of urinary excreted cortisol/cortisone metabolites. Administration of a HSD-1 inhibitor to such patients could reduce Cs morbidity via reduction of the cortisol (or HSD-1 metabolized medications, e.g., prednisolone) available to intracellular receptors. Furthermore, unlike current Cs treatments that are associated with substantial adrenal insufficiency risk, under full and sustained HSD-1 inhibition autonomously produced or ACTH-stimulated cortisol remains elevated in the circulatory pool, available to enter cells and act at GC, MC or non-genomic receptors at concentrations likely sufficient to prevent adrenal insufficiency. Those model predictions are under evaluation in ongoing Phase 2 clinical trials of the HSD-1 inhibitor SPI-62 in patients with ACTH-dependent Cushing's syndrome, autonomous cortisol secretion, and (in combination with prednisolone) polymyalgia rheumatica. Until further direct experience in these conditions is gathered, we still advise caution in patients with modest autonomous cortisol secretion, who may have suppressed ACTH and atrophied normal adrenal tissue, particularly in situations where stress-dose, non-precursor GC steroids should be considered (e.g., use hydrocortisone not cortisone acetate, or prednisolone not prednisone).

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EP858

Dual Endocrinopathy – a Case Vignette

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Initial Presentation (February 2018)
A 54 years old Chinese male attended the Emergency Department of a public hospital in February 2018 for psychotic symptoms of 1-month duration. He has a past medical history of bifrontal craniotomy 20 years ago for brain tumour. A computed tomography scan of the head was performed which showed increased pituitary fossa and suprasellar space soft tissue. A pituitary hormone panel was performed **[Table 1]**. He was diagnosed with Grave's disease and started on oral Carbimazole 5mg OM and given an Endocrinology outpatient appointment. Subsequent Follow Up (June 2018) He was seen in an Endocrinology outpatient clinic in June 2018 with the following blood test result [Table 2]. His Carbimazole was reduced from 5mg OM to 2.5mg OM.
Another Emergency Department Attendance (October 2018) He attended the Emergency Department of another hospital in Oct 2018 for headache & giddiness. A thyroid panel was performed **[Table 2]**. Evolving central hypothyroidoism with panhypopituitarism was suspected. A short synacthen test and a repeat pituitary panel confirmed this. Magnetic resonance imaging of the brain subsequently confirmed the presence of a pituitary macroadenoma.
Learning points
• This is a rare case of concurrent Grave's Disease and panhypopituitarism
• Interim treatment with carbimazole further confounded interpretation of the thyroid panel trend
• Long term treatment is unpredictable and will require close monitoring

Table 1

Hormonal Test	Reference Range	Results [Feb 2018]
8am Cortisol		
Adrenocorticotrophic Hormone (ACTH)	1.6-13.9pmol/l	404
Random Growth Hormone (GH)	<3.0 mg/l	0.07
Insulin-like Growth Factor 1 (IGF-1)	48-209 mg/l	<25
Follicle-Stimulating Hormone (FSH)	1.5-12.4 iu/l	0.8
Luteinizing Hormone (LH)	1.7-8.6 iu/l	0.1
Testosterone (bounded)	9.9-27.8 nmol/l	0.77
Thyroid Stimulating Hormone (TSH)	0.27-4.2 mIU/l	<0.005
Free Thyroxine (fT4)	12-22 pmol/l	24.1
TSH Receptor Antibody (TRAb)	<1.8 iu/l	3.5
Thyroid Peroxidase antibody (Anti-TPO)	5-34 iu/mL	175
Prolactin	86-324 mIU/l	808

Table 2

Hormonal Test	Reference Range	Results		
		Feb 2018	June 2018	Oct 2018
8am Cortisol		404	404	
Adrenocorticotrophic Hormone (ACTH)	1.6-13.9pmol/l	2.2	4.5	
Random Growth Hormone (GH)	<3.0 mg/l	0.07	<0.05	
Insulin-like Growth Factor 1 (IGF-1)	48-209 mg/l	<25	133	
Follicle-Stimulating Hormone (FSH)	1.5-12.4 iu/l	0.8	0.8	
Luteinizing Hormone (LH)	1.7-8.6 iu/l	0.1	0.1	
Testosterone (bounded)	9.9-27.8 nmol/l	0.77	0.34	
Thyroid Stimulating Hormone (TSH)	0.27-4.2 mIU/l	<0.005	0.160	2.61 [0.45-4.5]
Free Thyroxine (fT4)	12-22 pmol/l	24.1*	10.2*	5* [8-16]
TSH Receptor Antibody (TRAb)	<1.8 iu/l	3.5	-	
Thyroid Peroxidase antibody (Anti-TPO)	5-34 iu/mL	175	-	
Prolactin	86-324 mIU/l	808	790	

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EP859

The efficiency of treatment with growth hormone replacement therapy in children with idiopathic growth hormone deficiency in Albania

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Background
The idiopathic growth hormone (GH) deficiency is defined as the shortest height (-2 SD) without any further pathologies, including a detailed hormonal and radiological evaluation.
Objective and hypotheses
The evaluation of the efficiency of treatment with somatropin in children with idiopathic gh deficiency in Albania.
Methods
The study is based on the survey of 50 children of different ages, diagnosed with idiopathic GH deficiency by the pediatric endocrinology department of "Mother Theresa" University Hospital Center, excluding those children diagnosed with Turner Syndrome, chronic renal disease, GH resistance, SGA and IUGR. We evaluated the efficiency of the 1st, 2nd, 3rd-year treatment with somatropin, and measured the height (in cm/SD), the bone age, the values of GH and IGF-1, while using the Tanner-Whitehouse and Bayley-Pinneau method for the forecast of the height.
Results
The study involved 50 children, 43 male (86%) and 7 female (14%), who have showed up at the pediatrics ward between 2001- 2009. The median period of the treatment given was 4.6 years (3-10 yrs). The height at the moment the patients were first diagnosed was 118.3 ±13.1cm; after the 1st year of treatment with somatropin, the stature reached 129.7 ± 12.6 cm; after the 2nd year 137.8 ±12.3 cm and after the 3rd year, the height reached 144.9 ±12 cm. Growth velocity in the 1st year of the treatment was 11.4 ± 2.8cm/y, in the 2nd year it was 8.14 ± 2.13cm/y, while after 3 years of the treatment's initiation it reached 26.74 ± 5.4cm/y. The patients appeared to have a differentiation in height based on the Standard Deviation (SD) -4.6 SD ±1.2. The first year of the treatment saw an improvement in the patients' statures, with a SD of -3.4 ± 1.3 and it was found the most beneficial.
Conclusions
The study found that the first year of the treatment was the most beneficial for the patients'height growth, with the GH treatment not resulting in any major side effects.

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EP860

GH deficiency caused by a macroprolactinoma: difficulty of management

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Introduction
The use of GH treatment in patients with macroadenomas and GH deficiency is of concern to the clinician due to the theoretical stimulation of tumor regrowth by GH substitution. We report the case of an 18-year-old adolescent with a macroprolactinoma causing delayed stature and puberty.
Observation
We report the case of an 18-year-oldadolescent who consulted for gynecomastia with delayed stature and puberty. Physical examination displayed a statural delay of -3 standard derivation with a statural age of15 years. He had also pubertal delay and gynecomastia with Tanner stage of G2P2A1 The bone age was 13 years and six months according to the Greulich and Pyle method. The hormonal investigation showed markedly elevated plasma prolactine level of 4279mui/l. The evaluation of the other pituitary axes showed a normal thyroid function test. Therefore, it revealed a gonadotropic insufficiency (testosterone = 3.2mmol/l FSH = 3.28mui/ml LH = 1.23mui/ml) and a complete GH deficiency confirmed by 2 stimulation tests (insulin hypoglycemia test and clonidine test). The diagnosis of a macroprolactinoma was retained based on tumoral level of prolactinemia and pituitary magnetic resonance imaging revealing a pituitary macroadenoma of 10 mm long axis. The patient was put on a dopaminergic agonist: cabergoline 1.5 mg per week with good clinical and hormonal evolution. However, the difficulty was to substitute GH deficiency for fear of progression of the tumorous mass. It is the common opinion that GH substitution should not be consistently started in patients with macroprolactinoma for the reason that spontaneous recovery of hypothalamic pituitary function which has been inhibited by high PRL levels. But given the bone age limit and the non-promiscuity of the tumor and the optic chiasma, the decision was to initiate a recombinant GH treatment. The evolution was characterized by a good clinical response (gain of 11 cm in 9 months), without showing signs of tumor progression.
Discussion
In the literature, rare cases of combined treatment (dopaminergic agonist and somatotropin) have been reported but the treatment appeared to be effective in restoring growth velocity, also it seems to be safe as it did not show any progress on tumor growth. However, limited experience with the use of such combined therapy in children and adolescents warrants careful monitoring and on-going evaluation.

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EP861

A Case of Acute Psychosis Triggered by Anabolic Steroid Abuse

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Introduction
Professional athletes commonly use anabolic-androgenic steroids (AAS) to enhance performance. AAS include testosterone and its numerous synthetic analogs. AAS have numerous adverse effects among which central nervous system effects that include psychosis, delirium, mania and depression. Trenbolone is an AAS medication which is used in veterinary medicine for cattle muscle growth. What makes Trenbolone interesting is that it's also capable of inducing Selective androgen receptors modulators (SARM)-like effects. SARMs, as opposed to classic AAS, exert their action in a tissue-selective manner, providing the anabolic effects and suppressing the prostate adverse effects. However, Trenbolone remains different and needs to be evaluated through proper investigation. Herein, we report a case highlighting acute psychiatric effects of Trenbolone use in a young male.
Case Presentation
It's about a 20yo male, who was admitted in the orthopedics department for polytrauma after defenestration during a psychotic break. No personal or familial history of mental health issues or substance abuse were found initially. 2months prior to admission, the patient started to brutally present disorganized behavior and aggressiveness. He started experiencing persecutory, religious and messianic delusions, as well as auditive hallucinations. CT scan, liver sampling, renal function and thyroid hormones were normal. Blood numeration was normal excluding meningo-encephalitis. Blood and urine toxicology screen were normal. A testosterone dosage found low testosterone levels (3.51ng/mL). A hypogonadotrophic hypogonadism was confirmed via suppressed FSH and LH levels. Pituitary MRI was performed in order to exclude organic lesions, and was normal. All the available data were consistent with a chronic steroid intake. After multiple interviews, the patient confessed that symptoms started concurrently with Trenbolone intake. The first few days in orthopedics the patient appeared to be reluctant and disorganized, but after 2weeks he didn't display any psychotic symptoms or disorganized behavior. Testosterone levels returned to normal (5.5 ng/mL) after one month of intake. We concluded on a steroid-induced psychosis that we treated with 1mg risperidone.
Conclusion
AAS disturb the endogenous production of testosterone, which may persist months after drug withdrawal, thus explaining the low levels of testosterone in our patient. AAS can strongly affect the psyche and can induce psychotic features that are likely to be dose and drug dependent. In consequence, it's important to assess its mechanisms of action and subsequent symptoms to evaluate its safety.

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EP862

A polyuro polydipsic syndrome revealing a somatotropic adenoma in apoplexy: a case report

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Introduction
Pituitary apoplexy is an acute infarction and/or hemorrhage of the normal or tumoral pituitary gland. It is a rare mode of revelation of pituitary adenomas, and the only situation where the pituitary adenoma can be complicated by a diabetes insipidus.
Case report
Mrs Amina. Y, 54 years old, has been followed for 8 years for diabetes mellitus treated with metformin, and dyslipidemia under statins, presents in consultation for a severe polyuro-polydipsic syndrome, the urinary osmolarity was 95mOsmol/l confirming the diagnosis of diabetes insipidus. In her history, the patient reported a syndrome of intracranial hypertension with intense headaches, vomiting and visual disturbances dating back one month neglected by the patient and treated with analgesics. A cerebral MRI was performed, showing a pituitary macroadenoma in apoplexy, the visual field was affected, and the fundus was without anomalies. The workup showed a corticotropic insufficiency (cortisol level at 08h collapsed to 10 ng/l) and a thyrotropic insufficiency which were substituted. The patient was put on desmopressin with a good clinical and biological evolution. Regarding the secretory work-up, the clinical examination revealed signs in favour of an acrofacial syndrome (ring sign, change of shoe size). The IGF1 level confirmed the somatotropic character of the adenoma.
Discussion
Pituitary apoplexy is a rare but serious complication of pituitary adenoma. Considered as an emergency, Its clinical presentation associates a syndrome of intracranial hypertension, pituitary insufficiency and visual disorders that can go as far as blindness; brain imaging allows to confirm the diagnosis, and the treatment is urgent, based on hormone replacement therapy and tumor excision by Trans sphenoidal approach. Its onset is most often sudden and noisy, but more rarely, the remodeling, even massive, may be little or not symptomatic and the lesion revealed by visual disorders of progressive onset, by moderate headaches, intermittent or migraine-like, or even a secretory insufficiency as was the case in our patient in whom diabetes insipidus was the revealing element, which is the particularity of our observation.
Conclusion
The pituitary apoplexy is rare, but its gravity underlines the interest to think about it in front of any cranial symptomatology in the patients having a known pituitary adenoma, this reasoning becomes difficult, when the apoplexy is revealing, and even more difficult when the presentation is progressive and/or atypical, only the cerebral imagery, carried out in front of the slightest suspicion will make it possible to decide

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EP863

Prolactinoma and Pregnancy

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Introduction
Prolactin adenomas are the most common pituitary adenomas. Although the pituitary increases in size and the prolactinoma increase gradually during normal pregnancy; prolactinomas do not contraindicate pregnancy but require strict monitoring.
Goals
To study the impact of pregnancy on the development of prolactin pituitary adenomas.
Materials and methods
Retrospective descriptive cohort study conducted in the endocrinology department of the CHU Ibnou Rochd Casablanca in pregnant patients followed for prolactin pituitary adenomas
Results
We report 7 pregnancies in 5 women, whose average age is 33 years: there is a single micro adenoma and 4 macro adenomas, 4 patients had thyrotropic insufficiency and 2 patients had corticotropic insufficiency. The average duration of evolution before pregnancy was 4 years and all our patients were treated with cabergoline with an average dose of 1.5 mg/week. When the pregnancy was discovered, only one patient stopped the treatment. A pituitary MRI was performed on 3 of our patients during pregnancy objectifying a quasi-stable appearance of the adenoma. Two patients were complicated by gestational diabetes. The pregnancies were carried to term, vaginally in 3 cases and cesarean section in 3 patients ; 3 patients breastfed with good clinical evolution.
Conclusion
The evolution of prolactinomas during pregnancy is variable. This may justify the continuation of dopaminergic agonist treatment during pregnancy, with close monitoring.

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EP864

Pituitary apoplexy and prolactinomas. About a case series

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Introduction
Pituitary apoplexy describes the ischemic or hemorrhagic phenomenon that occurs in a previous pituitary adenoma. It may be the first manifestation of a pituitary gland adenoma.

Case 1
Female 31 years old macroprolactinoma in irregular treatment with cabergoline for three months Amenorrhea from the age of 14. Decreased visual acuity and oppressive headache. MRI pituitary apoplexy. Hospitalized and discharged with cabergoline and prednisone. Days later genital hemorrhage, a 12-week gestation was confirmed.
Case 2
Male, 40 years old. Two-month history of bitemporal hemianopsia, headache and nausea. MRI Pituitary apoplexy in a 3.5 cm adenoma. Prolactin >1000 ng/dl, other pituitary hormones decreased. Case 3: 53-year-old male, visual acuity deterioration and bilateral gynecomastia. Elevated prolactin. MRI Pituitary gland adenoma. Treatment with cabergoline is started. At 6 months improvement in visual acuity and decrease in prolactin level and tumor size. At 8 months, intense headache, vomiting and sensorium deterioration. New MRI: Extensive area of necrosis and intratumoral hemorrhage.
Discussion
We present 3 cases of prolactinomas that presented apoplexy due to pregnancy, large size of the adenoma and associated with treatment with cabergoline. The state of pregnancy is striking, although pituitary stimulation by estrogens. Its findings are truly exceptional. Another factor associated with pituitary apoplexy is large tumor although this association is generally more frequent non-functioning adenomas Dopaminergic agonists are risk factors for pituitary apoplexy, they cause lactotroph apoptosis. However, the frequency of this effect is rare, since they are drugs of choice in the treatment of prolactinomas.

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EP865

Asprosin, a novel adipokine, in the mouse hypothalamus: expression and *in vitro* effect on GT1-7 cells proliferation and GnRH secretion. Preliminary data

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Introduction
Asprosin, a novel adipokine, is a circulating hormone mainly secreted by white adipose tissue. Asprosin is encoded by the penultimate 2 exons of the fibrillin 1 (*FBN1*) gene. Protein product of *FBN1* is profibrillin-1, which undergoes a proteolytic cleavage by furin enzyme to produce mature fibrillin-1 and asprosin. Literature data indicated that asprosin is involved in the development of diabetes, obesity, cardiomyopathy, cancer, and polycystic ovarian syndrome. Moreover, asprosin is able to affect various cellular and physiological processes like appetite stimulation, insulin secretion, glucose release, apoptosis and inflammation through activation of Olfr734, an olfactory G-protein-coupled receptor. However, whether it can regulate the hypothalamic cells function has not been yet investigated. This study intended to examine *i*) the mRNA and protein levels of asprosin/Olfr734/furin in mouse hypothalamus and GT1-7 cells and *ii*) *in vitro* effect of asprosin on GT1-7 cells proliferation and GnRH secretion.
Materials and Methods
To measure the mRNA (real time PCR) and protein (Western blot) expression of asprosin/Olfr734/furin we used hypothalamus collected from C57BL/6J female mice at diestrous ($n=3$) as well as mouse hypothalamic GT1-7 cells. Moreover, immunolocalization of asprosin/Olfr734/furin were analyzed in GT1-7 cells. To study effect of asprosin on cells proliferation (AlamarBlue test) and GnRH secretion (ELISA), GT1-7 cells were cultured with recombinant mouse asprosin at doses 1, 10, 100 ng/ml. Statistical analysis was performed in Graph Pad Prism 7 software, using one-way ANOVA and Tukey's test ($n = 5$, $P< 0.05$).
Results
We demonstrated mRNA and protein expression of asprosin/Olfr734/furin both in mouse hypothalamic and GT1-7 cells. Moreover, we detected asprosin/Olfr734/-furin signals in GT1-7 cells. We noted a modulating effect of asprosin on GT1-7 cells proliferation and GnRH secretion.
Conclusion
Our preliminary findings suggest that the novel adipokine asprosin may play a regulatory role in the mouse hypothalamus.
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EP866

Immunotherapy-induced Endocrinopathy: A Case Report

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Introduction
Immunotherapy is an effective therapeutic choice increasingly prescribed in oncology. Endocrine toxicity is described among its side effects.
Methods
A case of a patient treated with immunotherapy since January 2022 is hospitalized in the endocrinology department in Bichat Hospital.
Results
Mr K, aged 46, treated with of anti-CTA4 and anti-PD1 inhibitors for melanoma. A month after the treatment the findings showed an acute adrenal insufficiency with a cortisol level at 14.9 nmol/l. An intravenous hydrocortisone treatment was initiated then relay orally. Besides, a Peripheral hyperthyroidism was noted (TSH was undetectable with FT4 at 3.5 N) secondary to Hashitoxicosis with anti TG and anti TPO antibodies at >10N, cervical ultrasound was normal. We opted for therapeutic abstention in view of the absence of clinical signs of hyperthyroidism. Prolactinemia was slightly elevated justifying the realization of MRI pituitary which was normal. The Control at 2 months showed: a cortisol at 584.9 nmol / L and ACTH at 22.7 pmol / l, the synacthen test showed the persistence of peripheral adrenal insufficiency with cortisol at T0 at 230 nmol /l, T60 at 261 nmol/l and AC TH at 50pmol/l hence the maintenance of hydrocortisone. Passage into peripheral hypothyroidism with TSH at 10N hence the treatment with Levothyroxine.
Conclusion
this case illustrates the possibility of occurrence of peripheral adrenal insufficiency under immunotherapy (less described in the literature than central involvement) justifying clinical and biological monitoring of the corticotropic axis throughout the duration of treatment with immunotherapy.

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EP867

Null cell adenoma: case report

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Introduction
Pituitary adenomas, more recently referred to as pituitary neuroendocrine tumors (PitNets) from other organs, are common neoplasms comprising 10 to 20% on intracranial tumors. Null cell adenoma is a diagnosis of exclusion that requires immunonegativity for all adenohypophyseal hormones and a lack of cell type-specific transcription factors. It represents 0,6% of all pituitary tumors.
Case
A 55 years old women with a history of treated thyroid vesicular carcinoma in remission currently. Followed for a geant agressif adenoma discovered following a headaches and a progressive decline in visual acuity associated with visual impairment (diplopia). The MRI (magnetic resonance imaging) of the sellar region had shown a voluminous endosellar process measuring 55x44x32mm, partially encysted with haemorrhagic changes, compressing the optic chiasm and invading the left cavernous sinus (KNOSP03). Hormonal workup revealed a serum prolactin level of 192ng/ml and gonadotropic deficiency. The ophthalmic examination found bitemporal hemianopia. The patient was then started on dopamine agonist (cabergoline) with a gradual increase in doses up to 3,5mg/week for two months. Then the patient only consulted a year later while having kept the same therapy. The MRI reveals a slight increase in the side of the process becoming KNOSP4. She had a transphenoidal adenemectomy. The histological analysis confirmed after three attempts a null cell adenoma (IHC for pituitary hormones and transcriptor factors). Four months later, the ophthalmic examination shown a stability and the MRI of the sellar region had shown the persistence of a voluminous tumor remnant discreetly lateralized on the left almost completely filling the optochiasmatic cistern, measuring 24x19 mm in the transverse axes, extended over a height of 32 mm, hyposignal in T1 and hypersignal in T2 wiehgted image, heterogeneous, enhanced discreetly and peripherally after injection of gadolinium salts.

Conclusion
Null cell adenoma represents a challenging diagnostic group of tumors. Close collaboration of the "pituitary team" is essential for a precise diagnosis and will contribute to the optimal treatment of the patient. New classifications, novel prognostics markers, and emerging imaging and therapeutic approaches will need to be evaluated to better serve this unique group of patients.

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EP868

Co-secreting TSH and GH pituitary adenoma

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Introduction
Thyrotropin-secreting pituitary tumors (TSH-omas) are a rare cause of hyperthyroidism and account for 0.5 to 3 percent of all functioning pituitary tumors and much less than 1 percent of all cases of hyperthyroidism. The co-secretion of thyrotropin (TSH) and growth hormone (GH) in pituitary adenoma is extremely rare. Only a few cases have been reported.
Observation
We report the case of a 40-year-old man who consulted an ophthalmologist for headache, and left monocular temporal hemianopia. A brain MRI revealed a 3 cm pituitary macroadenoma with an opto-chiasmatic impact. In front of this adenoma, a hormonal pituitary assessment showed a central hyperthyroidism with a high TSH level at 6.83 mUI/l and a high FT4 level at 42 ng/l, a co-secretion of growth hormone; GH level at 4.2 ng/ml, IGF1 level at 268,27 ng/mL and a failure of GH suppression at the oral glucose tolerance test, a gonadotropic insufficiency; FSH 0.9 UI/l, LH 1.2 UI/l, Testosterone 0.57 ng/ml, a reassuring cortisol level at 430 nmol/l and a normal prolactin level at 30 ng/mL. The patient was put under antithyroid drugs and referred to a neurosurgical center for a surgical treatment.
Conclusion
TSH-omas with associated hypersecretion of other pituitary hormones are found in 24.8% of cases. Hypersecretion of GH, resulting in acromegaly, is one of the most frequent associations (15.1%) along with prolactin secretion (8.4%). This may be explained by the fact that somatotroph and lactotroph cells share with thyrotropes common transcription factors. Surgery remain the usual first line of therapy, and further treatment by radiotherapy or somatostatin analogue is discussed case by case.

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EP869

Evolutionary and hormonal aspects after transphenoidal surgery for cushing's disease

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Introduction
Cushing's disease (CD), a hypercorticism caused by an ACTH-secreting pituitary adenoma, was associated with a 5-year survival of only 50%. Although advances in management have significantly reduced mortality, the results of transsphenoidal surgery, the gold standard in the treatment of CD, vary from patient to patient.
Objective
The aim of our study is to evaluate the results of transsphenoidal surgery in CD (evolution, complications) and to determine the factors that can predict this evolution.
Materials and Methods
This is a retrospective study of 12 patients hospitalized in the endocrinology department of CHU Farhat Hached, between 1987 and 2010 who underwent a transsphenoidal surgery for CD.
Results
Our sample consisted of 8 women and 4 men. The average age was 38.3 (24-48). Pituitary MRI came back normal in one case, revealed a microadenoma in 7 cases and a macroadenoma in 4 cases. Pathological examination confirmed the diagnosis in 8 cases, and 4 reports were unavailable. Remission was obtained in 6 cases (50%), Recurrence occurred in 3 cases (25%) with an average time frame of 8 years (3 -17 years), one of which benefited from radiotherapy with remission. Persistent disease was observed in 3 patients, one of whom was a candidate for revision surgery (the patient refused the operation), the other received radiotherapy without remission and died from complications related to hypercorticism. The third required simple monitoring. Two out of the 3 recurrences did not develop adrenal insufficiency (AI) while one developed transient adrenal insufficiency (with a recurrence time frame of 17 years), while 4 of the six remissions developed prolonged AI. Regarding complications of transsphenoidal surgery, there were two uncomplicated meningeal breaches, 3 cases of diabetes insipidus, one of which is definitive, and one case of sinusitis.
Conclusion
Transsphenoidal surgery is an effective means of treatment for Cushing's disease, however after successful treatment there is an increased risk of recurrence over time warranting prolonged lifelong follow-up. Subjects who have experienced postoperative adrenal insufficiency have a lower risk of recurrence, especially in case of a prolonged one. Depending on the postoperative biological findings, further treatment may be necessary (radiotherapy, surgery).

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EP870

A chordoma of the sphenoidal region: diagnostic challenge

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Introduction and Backgrounds
Pituitary adenomas emerge from the adenohypophysis and are confined to the region of the sella turcica, however, other sites may be involved as a result of extension infiltration, or ectopic location, the ectopic involvement of the sphenoid is rare.
Case Report
Our case illustrated a woman patient with an ectopic invasive macroprolactinoma diagnosed as a chordoma of the skull base. In Our case, the first histological examination was consistent with a coincidental Intrasellar Chordoma and Pituitary adenoma, Immunostaining was positive for synaptophysin and prolactin with a Ki67 index of 7%, suggestive of an invasive prolactinoma, in addition to the existence of vacuolated cells with foamy Cytoplasm resembling to hysaliphorous cells suggested the diagnosis of chordoma. However, immunohistochemical study using brachyury and S-100 protein have shown a negative stain. Thus, the diagnosis of chordoma was excluded.
Discussion and Conclusion
Thus, it is particularly important to maintain ectopic pituitary adenomas in sphenoidal or clival locations as the main differential diagnosis of chordoma; because the diagnosis can have significant implications on the management of the tumor, and can give us a golden opportunity for more conservative management (in our example managed with dopamine agonists), if the diagnosis can be made preoperatively rather than retrospectively based on histology.

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EP871

Reset Osmostat Syndrome: When Hyponatremia Become «A Normal». Diagnostics, Case Report

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Reset osmostat syndrome (ROS) is characterized by a change of normal plasma osmolality level (decrease or increase), which leads to chronic dysnatremia (hypo- or hypernatremia). We have described a Clinical case of ROS and chronic hyponatremia in a patient with chordoid glioma of the III ventricle. It is known that the patient had previously been diagnosed with hyponatremia (131-134 mmol/l). She has not hypothyroidism and hypocorticism. There is normal filtration function of the kidneys was (CKD-EPI 91.7 ml/mi/1,73m2). Urine osmolality and sodium level were studied to exclude of concentration kidney function disorder. During first three days after removal of the tumor of the third ventricle (chordoid glioma, WHO Grade II), the sodium level decreased to 119 mmol/l. Repeated infusions of 200-300 ml hypertonic 3% sodium chloride solution, gluco- and mineralocorticoid therapy was ineffective, increasing plasma sodium levels by 2-3 mmol/l with the return to the initial level during 6-8 hours. Hypopituitary disorders did not develop after surgery. With further observation, the sodium level remained within 126-129 mmol/l for 6 months after surgery. The water load test make exclude the classic syndrome of inappropriate secretion of

antidiuretic hormone, and confirmed the diagnosis of RSO. Because of absence of clinical symptoms associated with hyponatremia, no medical correction was required, patient was recommended to clinical follow-up.

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EP872

Central diabetes insipidus in adolescents : Not always a craniopharyngioma

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Introduction
Central diabetes insipidus reflects a serious underlying pathology in children. The etiologies are dominated in pediatric population by: central nervous system (CNS) tumors and malformations, histiocytosis, postoperative, radiation, and trauma injury to the hypothalamic-pituitary region. We report in this work three observations illustrating rare etiologies of pediatric central diabetes insipidus in the endocrinology-diabetology and nutrition department of the Mohammed VI University Hospital Center of Oujda in the eastern of Morocco.
Observations

Observation n°1
A 17-year-old female patient, with a history of influenza-like illness on probable COVID19 infection, admitted for exploration of a polyuria-polydipsia syndrome associated with headaches and significant decrease in visual acuity. An MRI of the hypothalamic-pituitary region has shown a hyperintense aspect of the pituitary gland on the T2 sequence with exaggerated enhancement of the gland after injection, pituitary height measured at 8 mm suggesting hypophysitis. The diagnosis was supported by the clear improvement both visually and diabetes insipidus after corticosteroid therapy.
Observation n°2
A 15-year-old female patient consulted for a polyura-polydipsia syndrome associated with headaches. An MRI of the hypothalamic-pituitary region has been realized showing an intra- and supra-sellar tumor process, with irregular contours, T1 isosignal, T2 hypersignal, heterogeneously enhancing and delimiting several cystic areas. A transphenoidal surgery was performed and the anatomopathological study came back in favor of a pituitary tuberculosis. The sputum testing for tuberculosis and quantiferon assay were negative, but the tuberculin skin testing was positive. The patient received anti-bacillary treatment with good evolution.
Observation n°3
A 15-year-old child with no notable pathological history was admitted for a polyura-polydipsia syndrome and secondary enuresis associated with frontal headaches. Biological explorations confirmed the central origin of diabetes insipidus. An MRI of the hypothalamic-pituitary region was performed showing a sellar mass in spontaneous T1 hypersignal, with a heterogeneous signal in T2, not enhancing after injection of Gadolinium, with a mass effect on the posterior pituitary, evoking a Rathke's cleft cyst in apoplexy.
Discussion-Conclusion
These three cases reflect the complexity of the diagnosis and the etiological polymorphism of central diabetes insipidus in children, making its management more delicate. Hence the interest of a meticulous etiological investigation in which hypothalamic-pituitary MRI plays an essential role, in the hypothesis of a tumoral lesion of this anatomical region.

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EP873

Diabetes Insipidus caused by autoimmune lymphocytic hypophysitis resulting in diagnosis and cure of Diffuse Large B-Cell Lymphoma

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Introduction
Association between lymphoma and pituitary dysfunction is well documented, though most commonly through mechanism of infiltrative pituitary metastasis, or primary lymphoma of the pituitary, rather than autoimmune lymphocytic hypophysitis. Here we present a highly unusual case whereby investigation into the cause of Diabetes Insipidus with radiological features of lymphocytic hypophysitis, led to diagnosis and cure of Diffuse Large B-cell lymphoma (DLBCL). Diabetes Insipidus with an MRI suggestive of autoimmune hypophysitis has been described. However, to our knowledge this is the first case where this presentation has been attributed to a paraneoplastic phenomenon.
Case Presentation
A 67-year-old lady presented to her GP with sudden onset polyuria and polydipsia associated only with a three-day headache. Her GP astutely diagnosed diabetes insipidus. MRI pituitary was highly suggestive of lymphocytic hypophysitis, with enhancement of the pituitary gland, thickening and heterogeneous enhancement of the pituitary stalk, and absence of posterior pituitary lobe T1 hyperintensity. Serum osmolality was 308 mosmol/kg; paired urinary osmolality was 132 mosmol/kg. Anterior pituitary function tests were normal. She experienced complete and instantaneous resolution of symptoms with Desmopressin. Comprehensive investigation into the underlying cause of her clinical and radiological presentation included CT Chest/Abdomen/Pelvis which revealed heterogenous sclerosis of multiple vertebral bodies. MRI whole spine demonstrated widespread bone marrow changes throughout the spine supporting a diagnosis of metastatic disease. Clinical examination remained normal. Myeloma screen and Mammogram were normal. Several attempts at vertebral bone biopsy proved unfruitful. PET-CT demonstrated multi-focal FDG avid sclerotic foci throughout the axial and proximal appendicular skeleton. No primary lesion or organomegaly was identified. Eventually, histopathology from a CT-guided biopsy of the left ilium revealed high-grade Diffuse Large B-Cell Non-Hodgkin Lymphoma of Germinal Centre Cell (GCC) type. She completed 6 cycles of R-CHOP chemotherapy. Subsequent PET-CT showed complete metabolic response.
Discussion
Differential diagnosis of hypophysitis is broad. In this case, we propose that DLBCL presented with paraneoplastic hypophysitis. Alternative serendipitous identification of concurrent DLBCL in a patient with autoimmune lymphocytic hypophysitis is possible. Initial MRI findings were typical of lymphocytic hypophysitis. Interval MRI four months later showed spontaneous regression of stalk changes, prior to lymphoma treatment commencing. Whilst low-grade lymphomas can be associated with waxing and waning phenomenon, this is not the case with CNS lymphoma. Paraneoplastic autoimmune hypophysitis is becoming increasingly recognised. Cases of anti-PIT-1 driven paraneoplastic autoimmune hypophysitis causing anterior pituitary dysfunction have been described. Paraneoplastic posterior pituitary dysfunction may be an emerging area of interest.

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EP874

Clinical and biological peculiarities of non-functioning pituitary adenomas in the Tunisian population: a monocentric study

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Background and Aim
Non-functioning pituitary adenoma (NFPA) is the second most common subtype of pituitary adenomas. This study aims to detail the clinical and biological particularities of NFPA in the Tunisian population.
Patients and Methods
A retrospective descriptive study of 35 patients followed for NFPA was conducted between 2000 and 2022 at the endocrinology Department of Hedi Chaker University Hospital, Sfax, Tunisia.
Results
The mean age was 52.1 $\pm$ 11.4 years with a male predominance (61.3%). The diagnosis of NFPA was motivated by tumoural syndrome in 77.4% of cases or by signs of hypopituitarism in 9.7% of cases. In 12.9%, it was an incidental discovery of a pituitary incidentaloma. The majority of NFPA were macroadenomas (90%). The initial clinical presentation was dominated by headache (90.3%) and visual impairment (80.6%). Visual field loss was observed in 30% of patients; 26.7% of them had bilateral visual field loss. In 3.2% of patients, NFPA caused bilateral blindness. The patients suffered from signs of pituitary insufficiency which could affect one or more axes: the corticotropic axis was the most affected (67.7%), followed by the thyroid (41.9%) and gonadotropic (41.9%) axes. Only 6.5% had somatotropic or lactrotropic insufficiency at the time of the biological evaluation. Disconnection hyperprolactinemia was observed in 26.7% with values exceeding 60 ng/ml in only 10% of cases.

Discussion
The diagnosis of NFPA is often delayed due to a long insidious evolution, especially in males. It is generally revealed by signs of tumor compression, sometimes severe, such as visual impairment, or by signs of anterior pituitary insufficiency. Surgery is the standard treatment. The earlier the diagnosis is made, the more complete the surgical resection will be.
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EP875

Prevalence and factors associated with pituitary apoplexy in non-functioning adenomas

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Objective
To determine the prevalence and the associated factors of pituitary apoplexy (PA) in non-functional pituitary adenomas (NFPA).
Patients and Methods
A retrospective analytical study of 35 patients followed for NFPA between 2000 and 2022 was conducted at our institution. A pituitary magnetic resonance imaging (MRI) scan was performed in all patients.
Results
The mean age was 52.1 ± 11.4 years, with a male predominance (61.3%). The primary reason for consultation was pituitary tumor syndrome (77.4%). Rarely, signs of hypopituitarism may inaugurate the clinical presentation (9.7%). Headache and visual disturbances dominated the initial presentation in 90.3% and 80.6% of cases, respectively. Underlying pituitary insufficiencies were frequently observed, namely those affecting the corticotropic (67.7%), thyroid (41.9%), and gonadotropic (41.9%) sectors. A pituitary MRI showed a macroadenoma in 90%. The prevalence of pituitary apoplexy in NFPA was 25.8%. Clinical factors significantly associated with PA were: inaugural hypopituitarism (OR = 0.22; $P = 0.018$), gonadotropic insufficiency (OR = 4.25; $P = 0.023$), lactotropic insufficiency (OR = 5; $P = 0.013$) and bilateral visual field amputation (OR = 1.636; $P = 0.049$). Tumor size > 4cm (OR = 0.19; $P = 0.011$) and the presence of hemorrhagic remodeling (OR = 5.83; $P = 0.001$) were also predictive factors of pituitary apoplexy.
Discussion
Pituitary apoplexy is the clinical expression of a hemorrhage and/or ischemia of a pituitary adenoma. This situation may require urgent surgical treatment. Our work allows us to identify patients with NFPA at risk of apoplexy based on several accessible clinical and radiological markers, such as tumor size > 4cm, the presence of inaugural hypopituitarism, and significant visual field amputation.
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EP876

Non-functional pituitary adenomas: management and therapeutic outcomes in the Tunisian population

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Objective
To assess the management and therapeutic outcomes of non-functioning pituitary adenomas (NFPA) in the Tunisian population.
Patients and Methods
We conducted a retrospective descriptive study of 35 patients followed for NFPA between 2000 and 2022 at the endocrinology department of Hedi Chaker University Hospital.
Results
The mean age was 52.1 ± 11.4 years, with a male predominance (61.3%). The majority of tumors were between 1 and 2 cm in size (46.7%). In half of the cases (53.1%), surgical treatment was performed. Pituitary apoplexy (35.3%), optic tract invasion (29.4%), and large tumor size (23.5%) were the main indications for surgery in our series. Tumour resection was often incomplete with remnants in 71.4%. The tumor residue size was > 3cm in 63.6% of the surgeries. Second-line treatment was indicated for 54.5% of patients, including re-do surgery (18.8%), radiotherapy (18.8%), or medical treatment (18.8%). No second-line treatment was performed in 45.5% of cases despite the persistence of a tumor remnant. Post-operatively, an improvement in visual disorders (53.8%) was generally obtained at the cost of stabilization or worsening of pituitary insufficiency in 92.4%. The average follow-up time was less than 5 years for 60% of our patients.
Discussion
Complete remission is difficult to achieve in NFPA compared to secreting adenomas. The recurrence and progression rate of NFPA after initial surgery varies from 15-66%. This rate may be reduced to 2-28% after adjuvant radiotherapy. Long-term clinical and radiological monitoring is strongly recommended.
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EP877

Growth hormone deficiency in pseudohypoparathyroidism type 1a: a case report

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Introduction
Pseudohypoparathyroidism (PHP) type 1a is a genetic disorder associated primarily with resistance to parathyroid hormone (PTH). Its pathogenesis has been linked to dysfunctional G-protein-mediated signaling. Since the G unit is an ubiquitary protein, its mutation can lead to variable hormonal dysfunction. In this context we report the case of a patient followed in our department for multihormone resistance.
Case report
A 9 years old boy, born at term to healthy consanguineous parents, presented to our department for delayed growth. Medical history revealed congenital hypothyroidism and PHP diagnosed respectively at 3 and 5 years of age. He was under supplemental calcium, active vitamin D and thyroid hormone replacement. Physical examination revealed a short stature with a height of 90 cm (– 3 s.d), signs of Albright hereditary osteodystrophy (AHO) and a scoliosis. Hormonal investigations revealed a partial growth hormone (GH) deficiency (GH peak at 6.58 ng/mL after propranolol-glucagon test), a hypocalcemia (1.64 mmol/l) contrasting with high PTH levels (68 pg/ml). The pituitary magnetic resonance imaging (MRI) was normal. Regarding the AHO features and the multiple hormonal resistances, PHP type 1a was suspected. In line with this hypothesis, the GH deficiency would be due to GHRH resistance. Genetic assessment of the GNAS1 gene, encoding the α-subunit of the G protein (Gαs) confirmed the presence of a missense mutation in exon 1 (c.154G > A, p.Glu52Ly). Treatment with recombinant GH was initiated and resulted in 7 cm gain within 7 months. At the most recent visit at the age of 10, both calcemia and TSH were within normal ranges.
Conclusion
We report a patient with PHP type 1a displaying PTH, TSH and GHRH resistance. Our case highlights the importance of GH status evaluation in all patients with known mutation in Gαs gene and supports the hypothesis that this mutation is the basis for multiple hormone resistance in pseudohypoparathyroidism. Further studies will be necessary to determine the possible beneficial effects of GH replacement in these patients.
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EP878

Clinico-biological profile of hypopituitarism associated with somatotropic adenomas

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Background and aim
Acromegaly is mostly due to a somatotropic adenoma. Regarding its insidious nature, this adenoma is often revealed at an invasive stage when one or more hormonal insufficiencies are already installed. This study aims to describe the clinical and biological features of hypopituitarism associated with somatotropic adenomas.
Patients and Methods
We conducted a retrospective study at the Endocrinology department of Hedi Chaker University Hospital, Sfax, Tunisia. We involved 29 patients diagnosed with acromegaly, whose clinical, biochemical, and imaging peculiarities were collected from medical charts.
Results
The mean age at diagnosis was 45.8 ± 12.4 years with a male predominance (51.7%). The mean duration of symptoms was 5.1 ± 5.4 years. Pituitary tumor syndrome (30%) and acrofacial dysmorphia (16.6%) were the main reasons for consultation. Signs of hypocortisolism were reported by 34.5% of patients, notably asthenia ($n=9$) or weight loss ($n=2$). Corticotropic insufficiency was biologically confirmed in 16.6% cases. Hypogonadism was clinically observed in 26.6%. Erectile dysfunction ($n=4$), secondary amenorrhea ($n=3$) and primary infertility ($n=1$) were the revealing circumstances. Biological exploration of the gonadotropic axis confirmed its insufficiency in 33.3%. Clinical hypothyroidism affected 13.8% of patients, with psychomotor slowing in the foreground ($n=4$). Thyroid insufficiency was found in 16.6% of cases. In our cohort, the hypopituitarism was dissociated in 40%, with a remarkable predominance of the co-occurrence of gonadotropic and thyroid insufficiency ($n=3$). Panhypopituitarism was noted in only one case.
Discussion
Various degrees of hypopituitarism may be present at the time of diagnosis of a GH adenoma, affecting up to ¾ of patients. The potential mechanism would be pituitary cell compression or destruction or even hemorrhagic necrosis. The gonadotropic sector is the first to be affected. The corticotropic and thyroid deficits seem to be delayed and more partial.

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EP879

Pituitary Tumours and Learning Difficulties-An Association or Incidental Finding?

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Introduction
Pituitary tumours one of the most commonly occurring intracranial neoplasms accounting for up to the 15 % of all intracranial neoplasms. Pituitary tumours are often associated with overproduction of hormones or, when they are large, they cause mass effect on surrounding neural structures which are adjacent to their typical location in the Sella turcica. Due to their multifaceted effects pituitary tumours may cause cognitive impairment due hormonal deficiency or mass effect on key cognitive areas of the brain. There is limited research on the impact of slow growing tumours and their impact on cognitive function.
Cases 1
A 26-year-old lady was admitted with general lethargy and leg swelling in her legs and being generally unwell. She had a history of epilepsy, long-standing amenorrhea and autism. Her hormone profile showed low cortisol level and hypopituitarism. she commenced hormonal replacement which improved her symptoms. MRI pituitary revealed a cystic pituitary mass with suprasellar extension (2.9x1.4 cm)

Blood test result table below

TSH	T4/T3	CORTISOL	LH/FSH	PROLACTIN
3.09	T4-3.2	14	LH 0.7, FSH 2	983

9/12/2022 SHORT SYNACTHEN TEST
ACTH-8
Cortisol-23
Cortisol 116
Cortisol-164

Case 2
A 20-year-old presented with right-sided visual dysfunction and headaches, diplopia and blurred vision in the right eye. There was no other focal neurology. He had history of Autism/learning disabilities diagnosed at age of 16 years. On examination, there was a partial right-sided third nerve palsy, with a fixed dilated right pupil. The right sixth nerve and fifth nerve showed no deficit. The fundi appeared within normal limits. MRI pituitary showed a large right-sided seller/cavernous sinus tumor partly cystic. The Sella was slightly enlarged at 12mm AP diameter. Normal biochemical hormonal profile. Admitted for Endoscopic Transsphenoidal Debulking of pituitary mass subsequently developed diabetes insipidus. He is on Desmopressin replacement and has achieved good fluid balance. Post-operative MRI was normal.
Discussion/Conclusion
Pituitary adenomas are slow-growing tumours that are classified basis of whether they secrete hormone or not. The benign nature of these tumours often means that they may be overlooked and remain untreated, with patients developing serious comorbidities that reduce their quality of life. Several studies have indicated that the physical compression from tumour might play a role in cognitive impairment as evidenced by the slow improvement observed post-surgical resection of tumour. We recommend doing MRI of the brain for patient with latent adolescent learning disabilities or difficulties

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EP880

What About Neuro-Endocrine Recovery After Pituitary Apoplexy?

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Introduction
Pituitary apoplexy is a serious medical complication of a pre-existing pituitary adenoma characterized by a variety of clinical symptoms ranging from mild headache to neurologically impaired and finally comatose patients.
Case report
We report a case of apoplexy in a large prolactinoma resulting in empty sella syndrome with a successful pregnancy. Our patient is a 31-year-old female, with a history of macroprolactinoma for approximately 7years. Who presented to our hospital with a history of severe headache, vomiting and visual disorders, she was pregnant in 24 weeks of amenorrhoea. The magnetic resonance imaging (MRI) was in favor of a stroke of the pituitary macro-adenoma. The hormonal exploration finds a corticotropic and thyrotropic insufficiency. A trans-sphenoid aspiration excision of the pituitary adenoma was performed urgently. MRI of control showed: total decompression of the optic chiasma. The patient had no further complaints during the pregnancy and at 38 weeks gestation she delivered a healthy baby.3months after delivery (7months after pituitary apoplexy), the pregnancy test was positive. An MRI was repeated which showed empty sella syndrome. The decision was to discontinue cabergoline and follow the patient regularly until delivery. The MRI was repeated and showed the same findings with a normal visual field test. The hormonal exploration showed nor mal thyrotropic function despite the withdrawal of substitution (the patient had stopped), and she still asymptomatic with a minimal dose of Hydrocortisone (5mg). This findings led us to discuss the recovery of hypothalamic pituitary axis ?. The hormonal tests are reported after delivery because our patient is currently pregnant in the first trimester.
Discussion
Pituitary apoplexy is a very rare cause of sudden headache in pregnancy and should be considered a medical emergency because of possible hormonal insufficiency. Surgery can significantly improve headache and both the endocrine and neuro-ophthalmic outcomes. Patients with severe neuro-ophthalmological deficits treated with early surgery can achieve an excellent recovery.
Key-words
Prolactinoma-Pregnancy-Pituitary apoplexy-Recovery

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EP881

Neuroendocrine neoplasms of the larynx: A small case series

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Introduction
Laryngeal neuroendocrine neoplasms are very rare malignancies comprising less than 1% of all laryngeal neoplasms.
Methods
Retrospective study including 5 cases of pharyngolaryngeal neuroendocrine tumors.
Results
The average age was 49 years ranging from 35 to63 years with a sex ratio of 4. The average consultation delay was 8 monthes. All patients patients were tobacco users. the chief complaint was dysphonia and dyspnea. Indirect laryngoscopy objectified a tumoral lesion arising from the left aryepiglottic region in one case, a tumoral lesion taking the 3 levels of the larynx with a fixed hemilarynx in 3 cases. One patient already had known lymph node involvement upon presentation. The staging assessment did not show distant metastases in all cases. The anatomopathological study of the biopsies with immunohistochemical analysis was in favor of a well-differentiated carcinoid tumor in 1 case, of small cell neuroendocrine tumor in 3 cases and of a poorly differentiated high-grade neuroendocrine in 1 case. Therapeutic management consisted of radio-chemotherapy in 2 cases, total laryngectomy in 2 cases and total pharyngolaryngectomy in 1 case. One patient developed locoregional recurrence and 2 distant metastases.
Conclusion
Laryngeal neuroendocrine tumors are extremely rare and heterogenous malignancies. It requires aggressive treatment and active follow-up.

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EP882

Clinical case of partially resistant prolactinoma

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In real practice, pituitary adenomas may have non-specific clinical manifestations. Patients are consulted by doctors of various specialties, but not endocrinologists. In confirmation of this we would like to present a Clinical case Male patient D. experienced severe headache at the age 39 y.o., was consulted by the neurologist. MRI demonstrated a pituitary macroadenoma 35x36x36 mm in size (22680 mm3) with supra-para-infrasellar growth. The neurosurgeon recommended surgical treatment. However, the patient referred to an endocrinologist. During the survey the patient noted that his weight has increased over the past 7 years by 20 kg, and his libido decreased. A hormonal examination showed very high levels of total and monomeric prolactin without any signs of hypopituitarism (see tab. 1). Cabergoline was prescribed in initial dose 0,5 mg/week. According to prolactin levels, the dose was up titrated to maximal 4.5 mg/week. The patient's condition improved during the first year of treatment: headache disappeared completely, body weight decreased by 8 kg, erectile function was restored. But normalization of the prolactin level was not achieved. Considering clinical improvement, decreasing prolactin levels and tumor volume, as well as the patient's desire, it was decided to continue drug therapy, the prolactin level and the adenoma volume gradually decreased. After 6 years of treatment (at the age of 45), prolactin level normalized for the first time. Total weight loss was 25 kg from the entire period of treatment. Tumor volume decreased by 82.5% compared with the parameter before treatment. The patient is currently taking cabergoline at the same dose of 4.5 mg (9 tabs)/week. Due to high dose of cabergoline, the patient undergoes echocardiography annually to exclude pathological changes in the valvular apparatus of the heart - no changes were noted.

Table 1

Parameter		Reference range
Total prolactin	**104700 mIU/l**	**39–422**
Monomeric prolactin	**98500 mIU/l**	**22–340**
IGF-1	284 ng/ml	111-284
TSH	0,923 mIU/l	0,4-4
T4 free	11,3 pmol/l	9-22
LG	1,24 mIU/l	1,14-8,75
FSG	1,23 mIU/l	0,95-11,95
Total testosterone	6,0 nmol/l	5,76-30,43
SGBH	16,7 nmol/l	13-71
Cortisol, 8.00	197 nmol/l	101–536
24-hour urinary free cortisol	406 nmol/l/day	138-524

Conclusions
1. This Clinical case demonstrates long term follow up male patient with partially resistant macroprolactinoma
2. Long-term use of maximum doses of cabergoline for 6 years was safe
3. The multidisciplinary approach to the treatment of patients with pituitary adenomas is necessary.

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EP883

Growth hormone deficiency and celiac disease: an association not to be missed

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Introduction
Celiac disease (CD) is an autoimmune enteropathy, induced by dietary gluten in genetically predisposed subjects, which manifests itself, most often, by digestive signs but also extra-digestive signs, in particular failure to thrive (FTT), nevertheless it is necessary to remain vigilant with regard to a real associated somatotropic deficit.
CASE
A 14-years-old male patient, followed for a celiac disease since the age of 6 years, under a strict gluten-free diet, referred to our consultation for a severe failure to thrive. A workup was performed in favor of low IGF1 level with complete insufficient Growth hormone (GH) response to insulin hypoglycemia test. In addition, the hypothalamic- pituitary MRI was in favor of pituitary hypotrophy. Growth hormone replacement therapy was initiated with good clinical outcome.
Discussion & Conclusion
The coexistence of CD and Growth Hormone deficiency (GHD) is rare and estimated at 0.02 to 0.26%. The GHD could be a result of CD or an association of the two conditions. The mechanism of the impairment of hypothalamic control of GH secretion is not very clear. Malnutrition could have a direct effect on the circulating gluten peptides in the brain, affecting the hypothalamic and pituitary control. Also, it has been suggested that a systemic autoimmune inflammatory reaction involving TNF-alpha could have a negative interference in growth. In the other hand, the presence of antibodies against the hypothalamus and the pituitary gland may be suggested as an autoimmune origin of this association especially in the presence of morphological findings on hypothalamic-pituitary MRI.

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EP884

Hypoplasia of the corpus callosum revealed by staturoponderal growth retardation: about a clinical observation

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Introduction
The corpus callosum is the most important of the interhemispheric commissures, its fibers called callosal radiations have a transverse direction. They connect different points of the neocortex. The corpus callosum represents the neopallial commissure; it has indeed a phylogenetic development modeled on that of the neocortex. Hypoplasia of the corpus callosum is included in a rare polymalformative syndrome characterized by agenesis of the corpus callosum (CC), distal limb anomalies, minor craniofacial anomalies and intellectual deficit.

Observation
We report the case of a girl aged one year and 2 months, referred to us at the endocrinology department for staturo-ponderal growth retardation, weight and height <-2 DS, with delayed psychomotor acquisition. In whom the clinical examination objectives: axial hypotonia, cleft lip and palate, delayed dentition = 2 lower and upper median incisors (corresponds to the development of a 7 months old baby), no low hairline, normal aspect of the OGE. A brain magnetic resonance imaging (MRI) was performed on her showing hypoplasia of the corpus callosum with partial agenesis of her knee, without any other anomaly of the brain parenchyma.
Discussion
In acrocallosis syndrome (ACS), craniofacial anomalies include macrocephaly with a prominent forehead and occiput, hypertelorism, a large anterior fontanel, a short nose with a wide nasal bridge and anteverted nostrils, and a short mandible. Anencephaly has been observed as well as supernumerary bone in the anterior fontanel, calvarial defect or Dandy Walker malformation. Hypoplasia or agenesis of the corpus callosum is the major characteristic sign of the syndrome. It may be associated with arachnoid cysts in about one third of cases and with various other cerebral anomalies (hypoplasia of the medulla oblongata, temporal lobe or bridge, micropolygyria and hypoplasia or agenesis of the cerebellar vermis with a characteristic "molar tooth" sign). The vast majority of patients have an intellectual disability which is severe in 80% of cases with a marked psychomotor delay. Hypoplasia of the corpus callosum is defined as thinning and/or narrowing of the entire corpus callosum. It occurs after the 20th week of gestation.
Conclusion
The corpus callosum plays an important role in the praxis and gnostic psychic functions that require the participation of both hemispheres; its fibers connect especially the associative areas. Its alteration plays a determining role in intellectual failure at its highest level.

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EP885

Crooke's Cell Adenoma:Aggressive Corticotroph Adenoma

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Introduction
Crooke's cell adenomas are nonneoplastic corticotropes with cytoplasmic accumulation of cytokeratin filaments in response to glucocorticoid excess. They are rare subtype of corticotrope adenomas presenting less than 1 % of pituitary adenomas.
Case
52 years old man attended Ophthalmology Clinic with 2 months history of right-sided reduced vision. He had a history of posterior polymorphous corneal dystrophy with a left corneal transplant and left cataract. As there was new bitemporal visual field loss, MRI was requested which showed a large pituitary macroadenoma (4x3x4 cm) with bilateral cavernous, sphenoid and ethmoid sinuses invasion with significant displacement of optic chiasm. Urgent endoscopic endonasal excision of the pituitary tumour was performed, however, due to size and location of the tumour, there was a limitation in safe resection and decompression of optic chiasm. Histology showed pituitary adenoma with focal expression of ACTH and high Ki67 index. Although the patient is obese with BMI of 45, there were no clinical signs of Cushing syndrome. After the operation, due to high ACTH 108 ng/l (reference range 0-46 ng/l), performed 24 hours urinary free cortisol and 1 mg dexamethasone suppression test which all came back normal. Repeated MRI three months after operation showed residual lesion involving sella, suprasellar cistern and left cavernous sinus with residual optic chiasm compression. He was referred to Neuro-Oncology team for consideration of radiotherapy due to ACTH expression and limited resection.47 GY radical radiotherapy was performed, unfortunately, MRI 3 months post radiotherapy showed an enlarged supra-sellar component to 17 mm from 12 mm with increased chiasmatic compression. Further endoscopic endonasal excision was performed and the patient become partial hypopituitarism requiring hydrocortisone and desmopressin replacement. The histology of pituitary adenoma is consistent with Crooke cell adenoma. Due to it aggressive nature, pituitary MDT suggested consideration for Temozolamide if further regrowth of the tumour. He then has two subsequent MRIs 6 months apart and remains stable appearances and is currently on regular MRI monitoring.
Conclusion
Crook's cell adenomas are aggressive in comparison to typical corticotrope adenomas. Most Crook's cell adenoma present as invasive macroadenomas with a high chance of recurrence therefore close surveillance is important for further management.

Pituitary profile blood tests were normal and the results were:

Tests	Results	Reference range
TSH	0.89 mu/l	0.34-5.6
T4	15 pmol/l	7.7-15.1
LH	4.6 iu/l	
FSH	7.6 iu/l	
Cortisol	319 nmol/l	
Prolactin	256 mu/l	55.4-276
Testosterone	5.8 nmol/l	8-22
IGF-1	20.8 nmol/l	6.3-27.4

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EP886

Acromegaly may be associated with gynaecological and skin forms of cancer

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Introduction
Acromegaly is a rare disease usually caused by growth hormone (GH) secreting pituitary adenomas (PA) and associated with a series of complications, including tumours. The most prevalent tumour types are colonic adenomas, colorectal cancer (1) and nodular goiter (2). We present two acromegaly cases attending our center that associate cervical cancer and another that associates melanoma.
Clinical cases

Case 1
A 56-year-old female patient diagnosed with GH secreting PA underwent two transsphenoidal surgeries, gamma knife radiosurgery and required treatment with lanreotide, pegvisomant and cabergoline to achieve biochemical control. Eleven years after diagnosis, the patient developed postmenopausal metrorrhagia; Pap smear and endometrial biopsy described *squamous carcinoma*. The patient underwent radical hysterectomy and pelvic lymphadenectomy. Histopathogical report (HP) showed poorly differentiated cervical squamous cell carcinoma – radiotherapy and cisplatin were then recommended.
Case 2
A 34-year-old female patient diagnosed with GH secreting PA underwent transsphenoidal surgery, gamma knife radiosurgery and necessitated lanreotide, pegvisomant and cabergoline to achieve biochemical control. Four years after diagnosis, the patient had a successful spontaneous normal pregnancy, followed by regular spontaneous menstruation. Six years later, the patient became spontaneously pregnant again, but the gynecological exam identified a 40 mm cervix lesion. Biopsy showed moderately differentiated *adenocarcinoma* – the patient underwent second-trimester therapeutic abortion, neoadjuvant radio-therapy, radical hysterectomy and pelvic lymphadenectomy. HP described chronic inflammatory ulcerative process.
Case 3
A 40-year-old female patient diagnosed with mixed GH and prolacting secreting PA underwent transsphenoidal surgery, high-voltage radiotherapy and achieved biochemical control under pegvisomant and cabergoline. Eight years after diagnosis, dermatology consultation recommended excision of two scapulae nevi. HP described *melanoma*, Clark level II.
Conclusion
Exposure to high levels of GH and Insulin-like growth factor I in acromegaly are potential contributors to cancer pathogenesis by endocrine and paracrine mechanisms (3). Further epidemiological studies are required to establish whether acromegaly would be associated with increased risk for cancer other than colonic and thyroid. Thus, cancer screening programmes designed for the general population are to be thoroughly applied in acromegaly patients.
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EP887

Non-secreting pituitary adenomas: clinical, biological, radiological and therapeutic aspects: a review of 17 cases

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Non-secreting pituitary adenomas (NSPA) are relatively rare benign tumors their prognosis depends essentially on their endocrine and ophthalmological repercussions the aim of our study is to outline their clinical, biological, radiological aspects, and the therapeutic choice.
Methods
Retrospective study of 17 patients with non secreting pituitary adenomas.
Results
We identified 17 patients with NSPA split into 12 women and 5 men with a sex ratio of 2.3. The average age was 47 years (+/-16.9). The circumstances of discovery were pituitary insufficiency in 17.6% of cases, an incidentaloma in 11.8% of cases, and a tumor syndrome in 70.6% of cases. Patients presented with headaches in 76.5% of cases and a decrease in visual acuity was noted in 64.7% of cases.47.1% of MRI cases were macroadenomas with invasion of the optic chiasma in 41.2% of cases. Necrotic remodeling was observed in 23.5% of cases and hemorrhagic remodeling in 17.6% of cases. The hypophysiogram study showed gonadotropic insufficiency in 47.1% of patients, followed by corticotropic insufficiency in 35.3% of cases. A hyperprolactinemia of disconnection was noted in 17.7% of the cases surgery was indicated in 36.4% of the cases given the damage of the optic chiasma the evolution during the follow-up was marked by the appearance of a pituitary deficit or more in 17.6% of the patients.
Conclusion
NSPA are most often discovered due to a tumoral syndrome, generating a pituitary insufficiency essentially gonadotropic and corticotropic. The operative indication is set according to the size, the evolutivity and the proximity of the optic tracts.

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EP888

Lymphocytic hypophysitis simulating a pituitary adenoma

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Introduction
Lymphocytic hypophysitis is a rare inflammatory disease of the pituitary gland of autoimmune origin, related to a diffuse infiltration of the pituitary gland sometimes leading to severe hypopituitarism. It is frequent in pregnant or postpartum women.
Case report
A 28 year old female patient, followed up for pituitary microadenoma with prolactin for 5 years under dostinex 1 tablet/week who reported headaches with visual acuity decrease with signs of corticotropic and gonadotropic insufficiency, pituitary MRI showed an intrasellar process of 3.6*2.5 mm, at FO : AV at 10/10 in ODG with diplopia, the CV was discreetly altered and the hormonal assessment objectified a corticotropic, and gonadotropic deficit. In the meantime, the patient presented for 1 year a polyuropolydipsic syndrome, the diagnosis of an osmotic polyuria following a hypercalcemia in the framework of a multiple endocrine neoplasia type 1 with pituitary adenoma was evoked but the calcemia was normal, the urinary osmolarity was low at 200 making evoke a polyuria insipidus a test of hydric restriction is planned. In view of this polyuropolydipsic syndrome of insipid appearance and the tumor syndrome which is not explained by the microadenoma, a lymphocytic hypophysitis was evoked and the workup was completed by antinuclear and anti-DNA antibodies.
Discussion
Lymphocytic hypophysitis is a rare autoimmune disorder predominantly affecting young women and is most often manifested by headache, visual disturbances or hypopituitarism. This observation shows the interest to think about it in front of a pituitary adenoma picture especially when it is a microadenoma not explaining the tumor syndrome and the polyuropolydipsic syndrome.

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Disease Control on Lanreotide in a Patient with Acromegaly

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Introduction
Medical treatment of acromegaly with somatostatin analogues (SAs) has been used for a long time and is a well-established treatment in cases where surgery, which is the first-line treatment, is impossible or inadequate. We report a case of acromegaly under control after initiation of Lanreotide.
Observation
Patient aged 59 years, referred for acromegaloid dysmorphic syndrome initially with tumor syndrome with IGF1 workup at 729 ng/mL (normal: 59 to 206) and at MRI presence of a pituitary macroadenoma with sphenoidal extension of "32 × 32 × 26 mm, enveloping the right carotid artery. In the workup, an unbalanced diabetes with HbA1c at 12% under insulin, a carpal tunnel syndrome confirmed by EMG, a sleep apnea syndrome and a colonic diverticulosis without any sign of malignancy, the rest is unremarkable. The patient underwent two neurosurgical operations. The last follow-up MRI showed no tumor residue contrasting with a still elevated IGF1 of 624 ng/ml. He was put on Lanreotide at a dose of 120 mg/mol. The evolution under treatment is marked by clinical improvement, decrease of the IGF1 level to 173 ng/mL with a control MRI still without tumor residue, as well as the balancing of diabetes with HbA1c at 6.5% under RHD, a regression of the carpal tunnel syndrome.
Discussion and conclusion
Although surgical treatment is the first line of treatment in acromegaly, treatment with SA is well established and is mainly used after insufficient surgical intervention, but also as primary medical treatment when surgery cannot be performed and finally when IGF1 concentration remains high despite the absence of tumor residue.

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EP890

Case report of a patient with paraganglioma diagnosed after surgery

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Introduction
Paraganglioma is a tumour derived from extra-adrenal chromaffin cells of the sympathetic paravertebral ganglia of the thorax, abdomen and pelvis. About 36 % to 60 % of the paragangliomas are functional secreting norepinephrine and normetanephrine, which cause hypertension. Non-functional paragangliomas can produce Chromogranin A. Paragangliomas also arise from the parasympathetic ganglia located along the glossopharyngeal and vagal nerves in the neck and at the base of the skull. Only about 5 % of these tumours secrete catecholamines.
Material and methods
The patient is a female, 51 years old. A few months before consulting the Endocrinology outpatient clinic, during an ultrasound examination of the abdomen, a tumorous lesion size 70 x 69 x 51 mm was detected - localized in front of the vena cava inferior. This finding was confirmed with Computed Tomography. She was not evaluated by an endocrinologist before the surgery. With a post-operative diagnosis of "St. post extirpationem TU v. cava inferior" and a histopathology report of paraganglioma, the patient consults the Endocrinology outpatient clinic: anamnestic without any symptoms both pre- and post-operatively and denial of past illnesses. From the outpatient laboratory analysis, metanephrine and vanillylmandelic acid in

24-hour urine were in the reference range and had an elevated value of Chromogranin A. A computed tomography scan of the abdomen and chest and a PET/CT scan with IV application of 18 F-FDG were performed, which did not reveal any local recurrence or distant metastases. During the follow-up, due to elevated chromogranin A values, a full body scan and SPECT/CT scan were performed after an i.v application of a somatostatin analogue. No pathological accumulations of a somatostatin analogue were registered.

Conclusion

Paragangliomas are rare neuroendocrine tumours. Malignancy is defined as the presence of metastasis at presentation or during follow-up, a metastasis is defined as the presence of chromaffin tissue in non-chromaffin organs. Paragangliomas commonly metastasize (30 %-50 %) to the liver, lungs, lymph nodes and bones. Metastases are usually functional, 80 % secrete norepinephrine and normetanephrine. It is essential that paragangliomas are acknowledged, because biochemical and imaging pre-operative evaluation is necessary, which is significant for perioperative and postoperative follow-up.

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EP891

Suprasellar Germinoma with Hypopituitarism and Central Diabetes Insipidus

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Introduction

Germinomas, which are the most common germ cell tumors of the central nervous system, may present with different symptoms depending on the location and are localized in the 20-30% suprasellar region. Here, we aimed to present a case of suprasellar germinoma with central diabetes insipidus, hypogonadism and secondary adrenal insufficiency.

Case Report

A 27-year-old male patient presented with dry mouth, polydipsia, polyuria and nocturia for 6 months. There were weakness, blurred vision and erectile dysfunction. Neurological and other system examinations were normal. He did not have a chronic disease and did not take any medication. There was a history of smoking. Laboratory examinations (Table-1) revealed central hypogonadism, low cortisol level and elevated prolactin. Hydrocortisone replacement was started due to secondary adrenal insufficiency in the patient who did not respond to the insulin tolerance test and glucagon stimulation test performed for secondary adrenal insufficiency due to low cortisol level. Fluid restriction test was performed due to low urine density; it was compatible with central diabetes insipidus and the patient was started on desmopressin. Pituitary magnetic resonance imaging (MRI) revealed a 12.2x12.7 mm suprasellar mass behind the pituitary stalk. There was no contact with the optic chiasm. On eye examination, the visual field and optic disc were normal. HCG level, a tumor marker, was high. The patient was consulted with medical oncology and neurosurgery; because the suprasellar lesion was in a risky location for resection, histological examination could not be performed and it was concluded that it was a germinoma as a result of radiological and biochemical evaluations. Since it is known that intracranial germinomas have high radiosensitivity, radiotherapy was planned for the patient in the first stage. In the follow-ups, it was observed that the disease activity decreased and the adrenal insufficiency and diabetes insipidus clinic regressed.

Conclusion

Germinomas are highly treatable lesions when diagnosed early. Since visual symptoms, endocrinopathies such as diabetes insipidus and hypopituitarism may be present in suprasellar lesions, they should be managed by a multidisciplinary team consisting of neurosurgeon, endocrinologist, ophthalmologist, radiation and medical oncologist.

Table 1 Laboratory Results

Parameter	Result	Referenge Range
Follicle Stimulating Hormone	<0.2 IU/l	1.27-19.26
Luteinizing Hormone	<0.2 IU/l	1.24-8.62
Total Testosterone	125 ng/dl	150-684
Prolactin	59.53 µg/l	2.64-13.13
Adrenocorticotrophic Hormone	33.7 ng/l	<46
Cortisol	11.32 µg/dl	
Thyroid Stimulating Hormone	0.81 mIU/l	0.41-6.80
Free T4	0.66 ng/dl	0.57-1.24
Urine Densitiy	1005	1010-1030
Human Chorionic Gonadotropin	38.7 IU/l	0-5

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EP892

A diagnostic dilemma

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Introduction

Nasopharyngeal carcinoma is a rare entity with a predominant geographic distribution in North Africa, Arctic, Southern China and Southeast Asia.

Case Presentation

32 yrs old, single, Saudi, male, had presented to our hospital on 26.11.2022. He had 2 months history of undocumented fever, blackish oral lesions, anorexia and profound weight loss(20kgs). He had become fully dependent and bed-bound. No addictions, allergies or high risk behaviours. Systemic review and family history-unremarkable. 7 yrs back, the patient had a road traffic accident with resultant left hemiparesis and aphasia, but was independent & mobile with support, till the current illness. On further evaluation, the patient was diagnosed to have poorly differentiated and metastatic Nasopharyngeal carcinoma [Vitally stable. GCS-E4M4V1 = 9/15, left sided flexion contractures & weakness. He was unkempt, markedly dehdrated & cachectic, with poor dentition & oral hygiene. Had blackish, necrotic lesions with crusting, over the dorsum of tongue, uvula & hard palate. CT scan brain, neck, facial bones(infiltrative and destructive nasopharyngeal & skull base soft tissue mass, invading sellar & suprasellar areas(1.5 x 4.7 cms), with erosion of the sella turcica and clivus. Besides, involvement of both cavernous sinuses, sphenoid sinus, left internal jugular vein, posterior nasal cavity, facial bones and bilateral retropharyngeal and left (necrotic) cervical lympadenopathy, was noted). CT chest-multiple indeterminate lung nodules, largest(13mms) in right lower lobe, suggestive of metastases. CT abdomen & pelvis-absent spleen, destructive bony lesions of right sacral ala and S1 vertebral body, suspicious of metastases. Multiple biopsies from the nasopharyngeal mass-poorly differentiated, Nasopharyngeal carcinoma (Negative for EBV, p16, fungal, TB & positive for CK 5/6]. He also had Panhypopituitarism (TSH 0.834mIU/l[0.25-5], FT4 9.42pmol/l[12-22], S. Cortisol AM 535nmol/l[137.9-686.7], Short Synecthen test normal, ACTH 0.33pmol/l(2.2-13.2), Prolactin 703mIu/l[86-324], LH 0.30mIU/l[1.7-8.6], FSH 2.34mIU/l[1.5-2.4], S. Testosterone 0.087nmol/l[8.64-29]). The patient had developed Cranial diabetes insipidus during hospitalization(with polyuria, S.Na + 156 mmol/l, Osmolality(-Serum312.19mOsm/kg [250-326], Urine185mOsm/kg[50-1400]). He was also found to have right corneal perforation with bilateral exposure keratopathy. Other significant laboratory derangements-normochromic anemia(Hb 10.4g/dl), hypoalbuminemia(S.Albumin 30.5g/l), deranged coagulation & Throat C/S + for Candida krusei & Yeast spp. He underwent emergent, right eye tectonic corneal grafting, bilateral amniotic memrane transplant and bilateral tarsorrhaphy. He was managed with Desmopressin, Low dose Thyroxine, maintenance steroids and an anti-fungal. The Tumor board consensus was to keep the patient on DNR status and for palliative care, in view of his Palliative performance scale(30%).

Conclusion

A multi-speciality team-work led to the exact diagnosis & the issues like corneal perforation, diabetes insipidus and Pan-hypopituitarism were addressed.

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EP893

A case of ectopic ACTH syndrome in squamous cell lung cancer

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Cushing's syndrome as a result of ectopic adrenocorticotropic hormone (ACTH) secretion, is associated with various tumors. Lung squamous cell carcinoma (LUSC) causing ectopic ACTH syndrome is a very rare condition. A 70-year-old male patient with a history of LUSC was admitted to our clinic for evaluation of worsening delirium and hypokalemia. Two courses of pembrolizumab were administered to our patient who was diagnosed with LUSC a month ago. At presentation, neurological examination revealed disorientation, agitation and

visual hallucinations. There were no signs of a Cushingoid appearance. Laboratory assessment showed a serum potassium of 2.8 mmol/l (3.1-5.5), glucose of 120 mg/dl (70-100), basal plasma cortisol of 39,3 µg/dl (6-18), ACTH 92,1 pg/mL (7,2-63,3) and post-1 mg dexamethasone serum cortisol 40,9 µg/dl. A high dose dexamethasone (8 mg) suppression test did not result in suppression of the cortisol levels (64,8µg/dl). Brain MRI was taken and no abnormality was detected in the pituitary gland. The patient's adrenal glands were evaluated as normal in the abdominal imaging. According to the results, the patient was diagnosed with ectopic ACTH syndrome. Metyrapone treatment was started to block cortisol secretion.

Key words
Ectopic ACTH syndrome, squamous cell lung cancer, delirium

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EP894

Clinical features and outcomes of an FSH-secreting pituitary adenoma: a case report

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Introduction
Pituitary adenomas are the most frequent sellar tumors in adults. Depending on their hormonal profile *in vivo* and on immunohistochemistry, they present different clinical profiles and progression outcomes. Thus, we report a case of an FSH-secreting pituitary adenoma.
Observation
The patient SG is 63 years old. He complained of intermittent headaches associated with a progressive decrease in visual acuity. Ophthalmological examination revealed bilateral papillary atrophy and visual field amputation. A pituitary MRI revealed a 23 mm pituitary macroadenoma responsible for a bulging sellar diaphragm and a rightward deviation of the pituitary stalk. It came into contact with the optic chiasm and engulfed both internal carotid arteries. The patient reported the onset of erectile dysfunction, decreased libido, and disappearance of morning erections without gynecomastia. The hormonal evaluation showed the integrity of the corticotropic and thyroid axis, a hypogonadotropic hypogonadism profile, and disconnection hyperprolactinemia (37.5ng/ml). Due to the threatened visual prognosis, the patient underwent surgery. Intraoperative observation highlighted the presence of a hemorrhagic tumor adherent to the lateral wall of the cavernous sinus which could not be completely resected. The anatomopathological study concluded with an FSH-secreting pituitary adenoma (FSHoma). Adjuvant external radiotherapy is recommended for this patient.
Discussion
FSHomas secrete increased gonadotropins and/or their subunits in an often biologically inactive form. Their clinical presentation is poor and remains dominated by the mass effect responsible for visual complications and signs of hypopituitarism. Surgery remains the only effective treatment option.
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EP895

Osteoporosis as a complication of acromegaly

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Context
Acromegaly is associated with many complications, which affects multiple systems, such as cardiovascular, respiratory, metabolic, muscles and bones. Osteoporosis and osteoporosis fracture are commonly neglected comorbidity of this rare disease. Usual manifestation of this skeletal complication is skeletal fragility and vertebral fractures, but prior research confirms, that other location fractures can be found as well.
Case illustration
We report the case of a 54-year-old woman, admitted with elevated blood pressure, hot flushes, episodes of intensive headaches, metacarpophalangeal joints pain, carpal tunnel syndrome, morning stiffness of joints. In 2018, laboratory test (increased insulin-like growth factor (IGF-1) 62,0 nmol/l (16,0 – 42,8)) in addition to clinical findings suspected acromegaly. MRI of the head was performed and pituitary macroadenoma was identified, size 34x46x35 mm, invading the left cavernous sinus. Histologically, macroadenoma was non-granulated with expression of Pit-1 transcription factor. Subtotal transsphenoidal adenectomy was performed in 2018. After surgery, somatostatin receptor ligand (SRL) Lanreotide 90 mg per week was prescribed, but IGF-1 concentration remained above normal range 42,1 nmol/l. Treatment was changed to Pasireotide LAR 40 mg every 28 days, but IGF-1 persisted uncontrolled. Patient started Cabergoline incrementally. Unfortunately, control head MRI demonstrated increased size of adenoma. In May 2020, according to the decision of multidisciplinary team, stereotactic radiotherapy surgery was performed. After surgery, Cabergoline 2 mg 2 times per week was continued. Six months after surgery IGF-1 level normalized – 22,7 nmol/l, growth hormone (GH) level remained increased 8,4 mU/l (0 – 6,3 mU/l). Eight months after radiosurgery patient admitted to the hospital with a fracture of the acetabulum, without dislocation, no surgery was required. The fracture occurred after a fall at home. DXA was performed, femoral neck T- score was -2,5. Osteoporosis was diagnosed. The patient was prescribed with Denosumab 60 mg every 6 months. No other bone fracture was registered since.
Discussion
Studies confirm that exceeded secretion of IGF-1 and GH enhances deterioration of bone and can lead to osteoporosis or even bone fractures. Unfortunately, the management of bone impairment in patients with acromegaly still need more attention, since the acknowledgement of this complication sometimes left forgotten.
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EP896

Polyuria-polydipsia syndrome : diagnosis approach through a case report

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Introduction
Polyuro-polydipsia syndrome (PPS) is defined by urine excretion rate more than 3L per day, associated with a parallel increase in oral fluid intake. It poses problems of positive and etiological diagnosis. We discuss in this observation the modalities of exploration of PPS and its main etiologies.
Case report
A 60-year-old patient, diabetic for 10 years, controlled on metformin, admitted for PPS evolving for 37 years. Clinical examination was normal. Considering a decrease in visual acuity, Pituitary-MRI was requested, which was normal. Blood glucose levels were between 0.9-1.5g/l, the calcium and phosphorus levels were normal. The basal Natremia was 137mmol/l and the basal urinary osmolarity was 180mosm/l. Water deprivation test was performed, and showed progressive urine concentration, decrease in hourly diuresis (250ml at H0 $=>$ 40ml at H5 and H6) and increase in urine osmolarity (181.7mosm/l $=>$387.2mosm/l). The test was stopped after H6 due to the patient's intolerance to thirst, thus the test was not completed by the administration of desmopressin. Copeptin measurement was not performed (unavailable). The diagnosis of primary polydipsia was retained and the patient was referred to the psychiatric department. During his follow-up, after 3 sessions of psychotherapy, we noted a clear clinical improvement (drinks: 7L/24h vs 19L/24h).
Discussion
Antidiuretic hormone (ADH) and thirst are the main determinants of water homeostasis. Disturbances of these regulatory mechanisms lead to PPS, which includes three different entities: central diabetes insipidus, nephrogenic diabetes insipidus, and primary polydipsia. Determining the correct diagnosis is crucial as

treatment strategies vary considerably. The first step in the diagnostic approach is to confirm PPS and to demonstrate its hypotonic or osmotic character. Water deprivation test combined with desmopressin administration is the diagnostic gold standard. However, it has several limitations and may not accurately distinguish patients with primary polydipsia from partial forms of central and nephrogenic diabetes insipidus. Direct measurement of ADH during the water deprivation test has not been widely adopted. Copeptin has been evaluated in PPS and appears to be a useful candidate biomarker for differential diagnosis. Pituitary-MRI is helpful to determine the possible etiology of central diabetes insipidus or if the water deprivation test is inconclusive. It is ordered as a first-line examination if the initial clinicobiological context already points to central diabetes insipidus.
Conclusion
Water deprivation test remains the "gold standard" for the etiological diagnosis of PPS. Copeptin could considerably improve the diagnostic accuracy of this test, thus allowing better management.

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EP897

Different etiologies of the endocrine hyponatremia

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Hyponatremia is the most common disorder of electrolytes encountered in clinical practice, occurring in 15-30% of acutely or chronically hospitalized patients. Although many cases are mild and relatively asymptomatic, hyponatremia is nonetheless important clinically because: acute severe hyponatremia can cause substantial morbidity and mortality; overly rapid correction of chronic hyponatremia can cause severe neurological deficits and death. We present Clinical cases of endocrine hyponatremia due to different etiologies.
Case I
48 y/o male was hospitalized in our clinic due to increased blood pressure, agitation and anxiety. Shortly after admission patient developed tonic-clonic seizure with suppression of cognition, bradypnea and was intubated. Lab work revealed very low sodium levels (Na-109 mmol/l). Patient's medical history reveals history of clinical depression, which was treated with SSRI. In 12.2022 he was consulted by an endocrinologist due to complaints of polyuria and polydipsia. Based on findings, patient was misdiagnosed with ADH deficiency syndrome (central DI) and was prescribed intranasal desmopressin. Preadmission clinical manifestations (polydipsia, polyuria) and laboratory findings (hyponatremia, low serum osmolality) correspond more with the diagnosis of primary polydipsia. Based on patient's objective findings, diagnosis was re-evaluated and proper medical treatment was initiated which led to improved outcome.
Case II
73 y/o female with multiple hospitalizations due to hyponatremia was admitted to our clinic due to complaints of weakness, confusion, nausea. Lab findings revealed hyponatremia, which was associated with quetiapine fumarate, prescribed by her psychiatrist, but switching her medication did not improve her sodium levels. Hyponatremia due to hypervolemia (CHF), SIADH induced by quetiapine fumarate were excluded. Further laboratory testing revealed secondary adrenal insufficiency. Head MRI showed pituitary microadenoma. Patient was prescribed hydrocortisone which markedly improved her overall condition with no further episodes of hyponatremia.
Case III
57 y/o female with a history of somatotroph adenoma was treated with transsphenoidal surgery. Few days after the surgery patient developed nausea, weakness and confusion. Lab assessment revealed hyponatremia. Diagnosis of SIADH was made and patient was instructed to restrict water consumption. In conclusion, the initial diagnostic approach to the adult patient with hyponatremia consists of a directed history and physical examination as well as selected laboratory tests. Some elements of the history, findings of physical exam, laboratory tests are usually already available, and guide the subsequent diagnostic approach.
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EP898

Acromegaly: Clinico-biological and radiological features

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Introduction
Acromegaly results from an autonomous hypersecretion of growth hormone (GH) typically by a pituitary adenoma, commonly revealed by a dysmorphic syndrome. The aim of our study was to describe clinico-biological and radiological features of acromegaly.
Methods
We conducted a retrospective study including 28 patients with acromegaly followed in the endocrinology department of Charles Nicolle Hospital. Clinical, biochemical, ophthalmological and imaging data were extracted from medical records.
Results
The mean age of our patients was 45,9 $\pm$ 13,9 with a sex ratio (F/M) of 1.5. Dysmorphic features, obesity, high blood pressure, electrical left ventricular hypertrophy, hepatomegaly, goiter and Galactorrhea were found in 96, 50, 61, 29, 25, 41 and 26% of cases, respectively. Obstructive sleep apnea was detected in 57% of patients. Pituitary evaluation showed corticotrop (41%), thyrotropin (19%) and gonadotropin deficiencies (67%). Disconnection hyperprolactinemia and cosecretion of prolactin were found in 33 and 4% of cases, respectively. Metabolic complications included diabetes (43%), prediabetes (36%), hypertriglyceridemia (57%), hypercholesterolemia (39%), low HDL-cholesterol level (73%), hypercalcemia (11%), hyperphosphoremia (29%) and hypercalciuria (22%). The median (IQR) GH was 24 (8-50) ng/ml. The mean size of adenomas was 20.4 mm [extremes :7mm-38mm]. Aggressive macroadenomas were detected in 14% of cases. Adenomas were invading optic chiasm (37%), cavernous sinus (30%) and sphenoidal sinus (11%). Tumor size was positively correlated with GH level ($r=0.731$, $P<$ 10-3) and negatively correlated with age ($r=$-0.387, $P=0.042$). Patients with aggressive adenomas were younger ($P=0.028$) and had lower cortisol levels ($P=0.002$).
Conclusion
The morbimortality of acromegaly is aggravated by its cardiovascular, respiratory, metabolic and ophthalmological complications that worsen the global prognosis.

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EP899

Ophthalmological complications in acromegaly

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Background and aim
Acromegaly is a rare condition caused by an excessive secretion of growth hormone (GH) and insulin-like growth factor1 (IGF-1), which are responsible for exaggerated somatic growth and cardiometabolic disturbances. This study aims to describe the ophthalmologic complications seen in acromegaly.
Patients and Methods
We conducted a retrospective study (1997-2020) at the Endocrinology department of Hedi Chaker University Hospital, Sfax, Tunisia. We involved 30 patients diagnosed with acromegaly, whose clinical, biochemical, and imaging peculiarities were collected from medical charts. All patients had an ophthalmologic examination with a visual field.
Results
The mean age of diagnosis was 45.8$\pm$12.4 years with a male predominance (51.7%). The mean delay of diagnosis was 5.1$\pm$5.4 years. Pituitary tumor syndrome (PTS) (30%) and acrofacial dysmorphia (16.6%) were the main reasons for consultation. Pituitary MRI revealed a somatotropic macroadenoma in 82.8% of cases. Visual disorders related to STH were noted in 42.8% of our patients, such as monocular blindness ($n=2$), diplopia ($n=4$) and visual blur ($n=7$). A decrease in visual acuity was observed in 21.4%. Ophthalmological examination revealed papilledema and optic atrophy in 10.7% and 7.1% of cases respectively. Bitemporal hemianospsia (14.3%) and temporal quadranopsia (3.6%) were the most common visual field alterations.
Discussion
Somatotropic adenomas are characterized by an insidious evolution and a mostly a delayed diagnosis. Visual disorders generally translate a tumoral invasion at the expense of the cavernous sinus and the optic tracts. The initial evaluation of the visual impact by an ophthalmologic examination, visual field and pituitary MRI is

strongly recommended. Preservation of the visual prognosis remains one of the major objectives of the treatment. A close collaboration between endocrinologist, neurosurgeon and ophthalmologist is necessary during all therapeutic steps.

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EP900

Pituitary Macroadenoma and hypercalcaemia - An association or an incidental finding?

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Introduction
Multiple Endocrine Neoplasms (MEN) are a group of rare hereditary tumours which have strong predisposition to endocrine organs. MEN1 is an autosomal-dominant inherited neoplasm with a broad genetic phenotype, characterised by synchronised or asynchronous triad neoplasms localised in the anterior pituitary, parathyroid and pancreas (Kamilaris and Stratakis, 2019; Li *et al*., 2022). Despite advances in the fields of diagnostic techniques and therapies, MEN1 continues to be associated with severe morbidity and mortality primarily due to malignant neuroendocrine tumours. Numerous combinations of both endocrine and non-endocrine manifestations have been described for MEN1 in literature (Singh, Mulji and Jialal, 2021; Newey and Newell-Price, 2022; Kamilaris and Stratakis, 2019).
Case report
61 year old lady presented to hospital feeling unwell and complaining of occipital headaches, visual disturbance, abdomen pain secondary to constipation, vomiting, and generalised body aches. She had extensive past medical history including permanent pacemaker inserted in 2017, ischaemic heart disease (NSTEMI 2016), aortic regurgitation with dilated ascending aorta measuring 48mm (2021), chronic kidney disease (stage 4), hypertension, obstructive sleep apnea, atrial fibrillation, and primary hyperparathyroidism. Her blood test on admission showed severe hypercalcaemia with serum calcium of 3.6, urea 8.1, creatinine 182 and elevated PTH. She was then commenced on IV fluids, and IV pamidronate to manage her calcium levels. CT head was done which showed a pituitary macroadenoma. The CT scan was reviewed by the neurosurgery team and with view surgical resection. In subsequent multidisciplinary team discussions, it was decided that transsphenoidal debulking of the suprasellar tumour was to be undertaken in order to preserve her remaining vision. She successfully underwent microscopic transsphenoidal debulking of the large pituitary adenoma on 29/07/22. She is currently on Hydrocortisone 10mg and Levothyroxine. Histological analysis of the biopsy revealed that the tumour had the following features: The tumour is overwhelmingly SF-1 positive, and there were several tumour cells with occasional LH and very rarely FSH positive. In addition, there are scattered populations of pit-1 positive cells within the tumour, and these correspond to TSH-positive labelling.
Discussion
MEN-1 is associated with a variety of non-malignant adenomas, the majority of these abnormalities are non-functional (Yoshida *et al*., 2011). It is widely reported that the vast majority of cases initially present with primary hyperparathyroidism. Nevertheless, the main neoplastic symptom patients present with is usually due to tumour mass effect, some tumours secrete chemicals that often result in manifestation of endocrine paraneoplastic syndromes (Li et al., 2022).

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EP901

Obesity prevalence in patients with acromegaly

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Background and aim
Acromegaly is a rare condition caused by an excessive secretion of growth hormone (GH) and insulin-like growth factor1 (IGF-1), which are responsible for exaggerated somatic growth and cardiometabolic disturbances. This study aims to determine the prevalence of obesity in patients with acromegaly
Patients and Methods
We conducted a retrospective study (1997-2020) at the Endocrinology department of Hedi Chaker University Hospital, Sfax, Tunisia. We involved 30 patients diagnosed with acromegaly, whose clinical, biochemical, and imaging peculiarities were collected from medical charts.
Results
The mean age of diagnosis was 45.8 ± 12.4 years with a male predominance (51.7%). The mean duration of symptoms was 5.1 ± 5.4 years. Acromegaly was due to a somatotropic adenoma in 96.7%. An exceptional case of ectopic secretion of GHRH by a pancreatic neuroendocrine tumor was reported. The average weight was 82.5 ± 13 Kg (extremes: 62-120 Kg). The average BMI was 28 ± 7.2 Kg/m^2(extremes: 17.5-40.5 Kg/m^2). The BMI was normal in 18.6% of patients while 40.7% were overweight. We report an increased prevalence of obesity of 40.7%. The mean waist circumference was 97.7 cm (range 75-129 cm) in men and 100.3 cm (range 85-129 cm) in women. An android distribution of fat was found in 11 patients (5 men, 6 women), a prevalence of 36.6%.
Discussion
GH and IGF-1 are counterregulatory hormones that antagonize the metabolic effects of insulin in the liver and adipose tissue, creating a state of insulin resistance and altering fat distribution in acromegalic patients. Adipose tissue hyperplasia-hypertrophy, related to GH/IGF-1 excess, would aggravate the risk of obesity in this population. These adipose disturbances can regress in 10% of cases after surgical treatment.

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EP902

Hyperparathyroidism and Prolactinoma: MEN1 or incidental association?

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Introduction
Primary hyperparathyroidism and prolactinoma can be associated as part of a MEN1. However, the association of the two pathologies can also be seen outside of a syndrome predisposing to endocrine tumors.
Case presentation
F.L., a 33-year-old woman followed for end-stage renal failure, during her follow-up hyperparathyroidism was discovered without any idea of the culprit and the victim: is the renal failure secondary to hyperparathyroidism or the other way around? The patient presented with severe headaches and bilateral blindness, an MRI of the pituitary was requested showing a pathological process of the base of the skull measuring 41 * 36.5 * 31 compressing the optic chiasm, and a biological assessment was performed with a prolactin level of 600 ng/ml. The diagnosis of prolactinoma was retained.
Discussion
MEN1 is an autosomal dominant disease due to a mutation of the MEN1 gene which codes for menin. Patients with MEN1 syndrome have endocrine (parathyroid, entero-pancreatic) and non-endocrine tumors (lipomas, angiofibromas, collagenomas, etc.). Primary Hyperparathyroidism is a common condition and less than 5% of cases are related to MEN1. It affects 90% of patients with MEN1, and Pituitary adenomas on the other hand affect about 40% of patients. These are often macroadenomas (85%). The predominant adenomas are prolactin adenomas (about 60%), and it is more voluminous than sporadic adenomas. Pancreatic involvement affects 75-90% of MEN1 carriers (multiple gastrinomas, multifocal insulinomas).
Conclusion
In our case, it is difficult to decide whether the association of prolactinoma and hyperparathyroidism is fortuitous or within the context of MEN1, especially since the primary origin of hyperparathyroidism cannot be confirmed.

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Reproductive and Developmental Endocrinology

EP903

Obesity, insulin resistance and hyperandrogenism are implicated in the progression of liver stiffness (LS) in women with PCOS

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Introduction
Non-alcoholic fatty liver disease (NAFLD) has become the leading cause of chronic liver disorders in Western countries, encompassing a spectrum of diseases ranging from simple steatosis to liver fibrosis and cirrhosis. Polycystic Ovary Syndrome (PCOS), the most common endocrine disorder of women during the reproductive period, is often implicated with NAFLD.
Aim
To investigate the potential involvement of PCOS on the aggravation of NAFLD by investigating the associations among insulin resistance (IR) or hyperandrogenism with the degree of liver fibrosis as expressed by liver stiffness (LS) and specific markers (hepatokines).
Methods
Forty-nine women with PCOS (based on the National Institutes of Health criteria) and 32 age- and BMI- matched healthy controls were included. IR was defined by the AUC-GLU, AUC-INS, HOMA-IR, QUICKI and FIRST-SECOND PHIS calculated from oral glucose tolerance tests. Hepatokines (fetuin-A, adiponectin, FGF-21) were measured. LS was assessed by Transient Elastography.
Results
For all participants, median age was 27 (range: 20-35) years, median BMI was 25 (19-35.2) kg/m^2 and median waist circumference (WC) was 94 (60-125) cm. All patients with PCOS had statistically significant greater LS values compared to controls (6.1 ± 0.9 vs 5.5 ± 0.9 kPa; $P=0.05$). According to BMI, patients and controls were subdivided in normal-weight controls ($n=14$; 17.3%), overweight controls ($n=18$; 22.2%), normal-weight PCOS ($n=26$; 32.1%) and overweight PCOS ($n=23$; 28.4%). Regarding LS, normal-weight PCOS, overweight controls and overweight PCOS, all had statistically significant greater LS values compared to normal-weight controls (5.5 ± 0.9, 6 ± 0.5, 6.2 ± 0.8 vs 4.7 ± 0.7 kPa, respectively; $P< 0.05$ for each comparison), whereas LS values were significantly greater in overweight PCOS compared to normal-weight PCOS (6.2 ± 0.8 vs 5.5 ± 0.9 kPa; $P< 0.05$). Statistically significant correlation was found between LS values and $\Delta4\alpha$ ($r=0.242$, $P=0.03$), but not with testosterone concentrations. Regarding LS and IR markers, statistically significant correlations were found in overweight PCOS between LS and AUC GLUC ($r=0.517$ $P=0.07$); in normal-weight controls between LS and adiponectin ($r=-0.537$, $P=0.05$), and in overweight controls between LS and HOMA IR, QUICKI, FIRST PHIS, SECOND PHIS, AUC INS, and adiponectin, respectively ($r=0.743$ $P=0.001$, $r=0.727$ $P=0.001$, $r=0.504$ $P=0.03$, $r=0.510$ $P=0.03$, $r=0.475$ $P=0.05$, $r=-0.646$ $P=0.04$, respectively).
Conclusions
PCOS and obesity are related to development of LS. The role of IR seems pivotal in the development of LS, whereas that of hyperandrogenism seems moderate. Interestingly, it appears that the co-existence of PCOS and obesity potentially promote more intensely the progression of LS.

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EP904

Morphofunctional and receptor status of endometrium in women with autoimmune thyroid diseases and pregnancy loss

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Objective
To determine the incidence of endometrium pathology in women with autoimmune thyroid pathology and history of reproductive losses, including an assessment of histological images and immunohistochemical (IHC) analysis of the endometrial receptor status.
Materials and methods
A prospective cohort study included a clinical and instrumental examination of 84 women aged 18 to 45 years with a history of 1 to 3 consecutive pregnancy losses. Patients were divided into 3 main groups: I - with primary hypothyroidism due to autoimmune thyroiditis (AITD) during drug treatment, II-euthyroid women with increased thyroid peroxidase antibody positive (TPOAb$^+$) titers, III- without thyroid dysfunction. The control group – IV($n=21$) consisted of women who have previously given birth and were planning pregnancy. To perform immunomorphological evaluation, we studied the results of endometrium biopsy, obtained using an aspiration curette (Pipelle) during the luteal phase of the menstrual cycle. As the second step, we used IHC analysis to evaluate the expression of steroid receptors (ERα, PR) in endometrial tissue.
Results
The study of endometrium aspiration biopsy identified high incidence of endometrium pathology in the main groups. In group I, the frequency of luteal phase insufficiency ($P=0.014$) was statistically significant in the context of unchanged progesterone serum level. IHC analysis found reduced expression of ERα in the stromal epithelium and glands in groups I and II as compared to group III ($P< 0.05$) and group IV ($P< 0.05$). Reduced indicators of PR expression were identified in stroma and glands in group I in comparison to other groups ($P< 0.05$).
Conclusions
Morphological changes of the endometrium and impairment of its receptor apparatus in women with either primary hypothyroidism due to AITD or with increased titers TPOAb$^+$ are a basis for considering this category of women high risk for an unfavorable outcome of pregnancy and for determining the appropriateness of their examination at the pregravid stage.
Key Words: pregnancy loss, autoimmune thyroiditis, immunihistochemical analysis, steroid receptors, ERα, PR.

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EP905

Olfactory bulbs and genetic defects in adolescents with Kallmann syndrome and normosmic hypogonadotropic hypogonadism

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Objective
To assess olfactory bulbs sizes and define the most common molecular defects in adolescents with congenital isolated hypogonadotropic hypogonadism.
Materials and Methods
Single-centre comparative study. 36 patients were included. The main group consisted of 21 patients with mean age of 15.9 years (17 boys, 4 girls) with congenital isolated hypogonadotropic hypogonadism (IHH): 13 - with Kallmann syndrome (KS), 8 – with normosmic isolated hypogonadotropic hypogonadism (nIHH). Kallmann syndrome was diagnosed due to complaints of hypo/anosmia. Olfactory bulbs width and height were assessed via MRI. Molecular-genetic studies were provided in all patients from main group. 15 patients were enrolled as controls (6 girls, 9 boys). Groups were matched for age, height and weight.
Results
Olfactory bulb malforrmations were founded in 20 out of 21 patients: bilateral olfactory bulb hypoplasia was diagnosed in 7, bilateral aplasia – in 4, unilateral hypoplasia – in 6, unilateral aplasia -2, aplasia of the one bulb and hypoplasia of another - 1. Olfactory bulb defects were found in 7 out of 8 nIHH children with no complains of hypo/anosmia. Height and width of olfactory bulbs were significantly smaller in main group in comparison with controls ($P< 0.05$ via Mann–Whitney U test). Median of right bulb height was 1.0 mm [0.2;1.2] in patients from the main group vs. 3.0 [2.5;3.2] in control group. Median of right bulb width was 1,0 mm [0.2;1.7] in patients from the main group vs. 2.5 [2.0;3.0] in control. Median of left olfactory bulb height was 0.8 mm [0.0;1.1] in main group vs. 3.0 [2.7;3.2] in controls. Median of left olfactory bulb width was 0.4 mm [0.0;1.1] in main group vs. 2.5 [2.0;3.0] in comparison with control group. There were no statistically significant differences in olfactory bulb sizes between patients with KS and nIHH ($P> 0.05$). Molecular defects were identified in 9 patients: defects in FGFR1 were found in 4 out of 9 patients, CHD7 - 3, KAL1-1, FGF17 - 1. 5 defects were identified as variants of uncertain significance, 2 as likely pathogenic and 2 as pathogenic.
Conclusion
Bilateral olfactory bulb hypoplasia is a reliable sign of hypogonadotropic hypogonadism: it was identified in every third adolescent with congenital IHH. All pathogenic genetic variants were in FGFR1 and were associated with

uni/bilateral olfactory bulbs hypoplasia. Normal sense of smell doesn't rule out olfactory bulbs defects.

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EP906

Individuals treated for gender dysphoria with medical and/or surgical transition who subsequently detransitioned: a survey of 7 detransitioners

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Introduction
Detransition is the act of stopping or reversing a gender medical, social or surgical transition. The study's purpose was to describe our experience with a group of transsexual people in detransition phase.
Material and methods
A cohort of 204 people with gender incongruence attending the Identity Gender Unit Hospital Clinico of Valladolid from January 2014 to December 2022 was studied. Seven of those participants detransitioned and were asked for their reasons, gender identity in detransition phase, and which social, medical, and surgical steps they took to detransition.
Results
Seven detransitioners were natal male. At the beginning of the detransition the age was 24[14-43] years and at started transition was 17[15-19] years. They remained transicioned for a duration of 2 [1-29] years. Most (6/7) had transitioned both medically and socially. Three also had surgical transition (mammoplasty). Mental health diagnoses before the onset of transition was: Anxiety (1/7), Eating disorders (1/7), Autism spectrum disorders (2/7). The mayority (4/7) received an adequate evaluation from mental health professional before starting transition and psychological support during transition. Reasons for destransition included: change in gender identity (3/7), satisfied (1/7) and dissatisfied (1/7) by the physical results of the transition, exploring alternative non-medicalised ways of living their identities and bodies (2/7). Nearly all participants medically detransitioned by ceasing cross-sex hormones (6/7). At the time of detransition 4/7 maintain a female gender identity and reports no gender dysphoria. Only two detransitioners were dissatisfied with their decision to transition and five were satisfied with their decision to detransition.
Conclusion
There are many different reasons and experiences leading to detransition. Medical detransition following the reaffirmation of a transgender identity is not uncommon. Comprehensive care by a multidisciplinary and experienced team is essential.

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EP907

Synergy between vitamin D and estradiol in PCOS patients affected by COVID-19 infection

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Introduction
Polycystic ovary syndrome (PCOS) affects 5-10% of reproductive aged women. PCOS also manifests a chronic pro-inflammatory state. Estradiol is known to modulate the actions of immune cells, and, therefore, the antiviral mechanisms of these cells could also be modified by this hormone stimulus. In the presence of vitamin D, the binding energy of the spike protein to ACE2 was increased and transferring Apo to Locked S conformer of spike trimer was facilitated. Together, the interaction between spike protein and ACE2 can be disrupted by vitamin D. Potential use of estradiol and vitamin D to reduce virus invasion and replication needs clinical investigation.
Aim
To evaluate the relation between vitamin D and estrogen in PCOS women affected by COVID-19 infection.
Methods
A cohort observational study was conducted. Of the total of 283 PCOS women, 129 affected by COVID-19 infection between March 1, 2021. to June 30, 2022. Ninety-two of them were included in the study. Inclusion criteria were no supplementation with Vitamin D and estrogen, and SARS-CoV-2 test positive. The control group involved 59 PCOS patients not affected by COVID-19. Serum 25-hydroxyvitamin D (vitamin D), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lipid profile, fasting serum glucose, basal insulin, homeostasis model analysis of insulin resistance index (HOMA-IR), TSH, PRl, FSH, LH, 17β-estradiol, and total testosterone were determined. The main outcome were Vitamin D and estradiol levels in PCOS patients with COVID-19 infection compared to women without COVID-19 infection, categorized into mild, moderate, or severe infection according to WHO classification.
Results
After adjusting for age, BMI, insulin resistance and smoking status we found an association between low estradiol and vitamin D, and risks for COVID-19 adverse outcomes. In the fully adjusted model, PCOS women with low vitamin D and low estradiol had a 22% increased risk of COVID-19 (HR: 1.25 (1.05-1.46), $P = 0.01$).
In conclusion
It is tempting to hypothesize that the synergy between vitamin D and sex hormones could contribute to the COVID-19 outcome in PCOS patients.

Keywords: COVID-19, polycystic ovary syndrome, estradiol, vitamin D
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EP908

Assessment of Social Functioning in People with Female-to-Male Gender Dysphoria

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Background/Aim
In literature, many previous studies adressed that Gender-affirmig Hormone Therapy (GAHT) improves the factors affecting social functioning such as self-esteem, mental well-being, behavioral health and quality of life. In this study, we aimed to quantitatively evaluate the effects of the GAHT on social functioning using a psychiatric scale in people with female-to-male (FtM) in Türkiye.
Methods
The single center, cross-sectional study included 77 people with FtM Gender Dysphoria (GD) who were followed-up with for GAT at the Psychiatry or Endocrinology, Metabolism and Diabetes outpatient clinics, between January and April 2022. The sociodemographic data form and Social Functioning Scale (SFS) were used. Informed consent was obtained from all individual participants included in the study. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 21.0).
Results
We examined a total of 77 people with FtM; 41 had received GAHT and 36 had not received GAHT with a mean age of 24.7 $\pm$ 4.5 years. In people with FtM who received GAHT, 75.6% had received hormone therapy under the supervision of a doctor and the median duration of the hormone therapy was 12 (IQR = 5-36) months. When the SFS scores are evaluated from the point of GAHT, people with FtM who received hormone therapy had more social functioning than those who did not, with regard to the SFS total ($P = 0.01$), social engagement/withdrawal ($P = 0.001$), interpersonal behavior ($P = 0.002$) and pro-social activities ($P = 0.027$) subscales scores. On the other hand, people with FtM who undergone bilateral mastectomy had higher scale scores that predicted more social functioning than those had not. Finally, the SFS total ($r = 0.272$, $P = 0.017$), pro-social activities ($r = 0.239$, $P = 0.036$) and recreation ($r = 0.236$, $P = 0.039$) subscales scores were positively correlated with real-life experience in people with FtM.
Conclusions
The findings of our study indicate that people with FtM GD receiving GAHT and/or undergoing bilateral mastectomy have a significantly increased social functioning. As expected, it can be said that the real-life experience is effective on social functioning in these people.

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EP909

Dose-related risk of hypertension development in young female transgender patients treated with cyproterone acetate

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Introduction
We have recently reported that the use of cyproterone acetate (CPA) is associated with a highly significant increase of the risk of hypertension development after 5 years (adjusted hazard ratio 0.227, $P < 0.001$) in young transgender women. Due to the risks associated with the prolonged use of CPA (including the development of meningioma), the EMA presently recommends avoiding the use of doses > 10 mg CPA daily if possible. In fact, acceptable efficacy for androgen blockade in female transgender people has been reported with doses as low as 10 mg daily, but in our country the only available presentation is a 50 mg pill and dosages < 25 mg daily are impractical, while the standard protocols recommend doses up to 100 mg daily, depending on the clinical and analytical results.
Methods
Retrospective review of the clinical records of the transgender women < 30 years old, treated with CPA plus estradiol and followed for 5 years, stratified according to their cumulative dosage of CPA:
- A: up to 6500 mg (mean up to 25 mg/day)
- B: 6501 to 13000 mg (mean >25 -50 mg/day)
- C: 13001 to 18500 mg (mean >50-75 mg/day)
- D: 18501 to 26000 mg (mean >75-100 mg/day)

Hypertension was diagnosed when a repeated clinical sitting BP ≥ 140/90 mmHg or ambulatory (ABPM or systematic HBPM) ≥ 135/85 mmHg was present in a previously normotensive patient. All patients gave their informed consent.
Results
Data from 56 transgender women continuously treated with CPA + estradiol for at least 5 years were obtained. The adjusted yearly hypertension incidence was 4.96% vs. 0.98% in women treated with estradiol without androgen blockade. There were 6/25/18/7 patients in the strata A/B/C/D and their adjusted yearly hypertension incidence was 2.3%/4.2%/5.9%/7.6% ($P < 0.001$ for the difference).
Conclusions
There is a clear-cut dose dependence in the development of hypertension associated with CPA + estrogen treatment in young transgender women. However, even relatively low (up to 25 mg/day) dosages of CPA are apparently associated with significantly increased risk of hypertension development. Considering also other risks associated to the CPA plus estradiol combination (meningioma, obesity, depression, low libido, liver toxicity, thrombophilia, hyperprolactinemia...), we conclude that the use for this indication should be reconsidered. We cannot however exclude that very low dosages, in the order of 10 mg/day, may be safe for hypertension development.

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EP910

Undercarboxylated Osteocalcin/GPRC6A: A Bone Testis Crosstalk

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Purpose
Undercarboxylated-Osteocalcin (ucOCN), acting on its putative receptor GPRC6A, was shown to stimulate of testosterone (T) production by Leydig cells in rodents, in parallel with the hypothalamus-pituitary-gonadal axis (HPG) mediated by luteinizing hormone (LH). The aim of this cross-sectional study is to evaluate the association among serum ucOCN, *rs2247911* polymorphism of GPRC6A gene and the endocrine/reproductive pattern in a cohort of infertile males, possibly identifying an involvement of the ucOCN-GPRC6A axis on testis function.
Methods
172 males, including 74 oligozoospermic, 58 azoosperminc patients and 58 normozoospermic controls, were prospectively recruited at the Orient Hospital for Infertility, Assisted Reproduction and Genetics in Syria (Study N. 18FP), from July 2018 to June 2020. Outpatient evaluation included the clinical history and anthropometrics and a fasting blood sampling for hormonals, serum OCN (both carboxylated and undercarboxylated), glycemic and lipid profile and screening for *rs2247911* GPRC6A gene polymorphism.
Results
Higher serum ucOCN associated with higher T and HDL-cholesterol (respectively: $r = 0.309$, $P < 0.001$ and $r = 0.248$, $P = 0.001$), and with lower FSH ($r = -0.327$, $P < 0.001$) and LDL-cholesterol ($r = -0.171$; $P = 0.018$). Patients bearing the GG genotype of *rs2247911* had higher sperm coung compared to GA genotype ($P = 0.043$) and, compared to both AG and AA genotypes, higher serum T ($P = 0.004$, $P = 0.001$) and lower triglycerides levels ($P = 0.002$, $P < 0.001$). Upon normalization for LH levels and body mass index, *rs2274911* and ucOCN were significantly associated with higher serum T at linear stepwise regression analysis ($P = 0.013$, $P = 0.007$).
Conclusions
Our data suggest the involvement of ucOCN-GPRC6A axis in the regulation of T production by the testis complementary to HPG.

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EP911

Position and Characteristics of adolescents diagnosed as PCOS under the original Rotterdam criteria but excluded under the 2018 updated guideline

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Background and Aims
Polycystic ovary syndrome (PCOS) usually develop symptoms during adolescence. However, diagnosis in adolescents is challenging because physiologic development overlap typical manifestation of PCOS. Recently, an international evidence-based PCOS guideline development group recommended that ultrasound should not be used for the diagnosis of PCOS in those with a gynecological age of < 8 years. Thus, girls with irregular menstruation (IM)/PCO or hyperandrogenism (HA)/PCO cannot be diagnosed as PCOS if they do not pass 8 years since menarche. This study aimed to investigate the characteristics of these excluded girls.
Methods
We included subjects who were between 2- 8 years since menarche. Adolescent PCOS ($n = 315$) was diagnosed according to the 2003 Rotterdam criteria like adults. A total of 428 girls served as controls.
Results
In 315 girls with PCOS, numbers of the IM/HA/PCO, IM/HA, HA/PCO and IM/PCO phenotypes were 206 (65.4%), 30 (9.5%), 12 (3.8%) and 67 (21.3%), respectively. According to the 2018 guideline, 79 girls (25.1%) with HA/PCO (15.2%) or IM/PCO (84.8%) phenotypes are not diagnosed as PCOS. These girls who had changes in diagnostic status were designated as “increased risk” group. As expected, PCOS group showed the worst metabolic profiles (degree of generalized and central obesity and frequency of IR, prediabetes or diabetes and metabolic syndrome) and a higher hirsutism score than those of the other two groups. About 90% of the “increased risk” group were lean, which was similar to the controls. However, they showed worse metabolic profiles (mean BP, TG, fasting insulin and HOMA-IR levels) than did the controls, but showed similarly elevated profiles with those of PCOS. The “increased risk” group showed similarly elevated serum LH levels and LH/FSH with those of the PCOS.
Conclusions
One-fourth of the adolescent girls who were diagnosed as PCOS based on the original Rotterdam criteria were excluded from the diagnosis of PCOS using the 2018 guideline. Although these ‘increased risk’ girls do not fulfil the diagnostic criteria of PCOS, they visited hospital due to menstrual abnormality or hyperandrogenic symptoms, and showed significantly worse metabolic and androgenic profiles than did controls. And they shared considerable metabolic and hormonal features with PCOS. About 90% of ‘increased risk’ girls were lean, but they were not metabolically reassuring group. A practical approach to them would involve controlling symptoms and regularly evaluating them regarding newly-developed or worsening PCOS-related symptoms or metabolic abnormalities.

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EP912

Quantification of miRNAs (miR4743-5p, miR149-5p, and miR331-5p) in the placenta of south Indian pregnant women with Early and Late onset of Preeclampsia

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Background
Preeclampsia (PE) is a multifactorial and multisystem disorder, with unknown pathophysiology, but factors such as defective trophoblast invasion and narrowing of spiral arteries may be contributing to the onset of PE and affecting mother and foetus development. Early prediction of PE may improve the surveillance and prognosis of hypertension in pregnant women in preventing associated complications. Therefore, it is essential to find markers for the detection of PE in the pre-symptomatic stage and miRNA can be considered as biomarkers for early diagnosis.
Objectives
To create complete profile of miRNA with the help of next-generation sequencing in placental tissues collected from Early Onset of Preeclampsia (EOPE; $<$ 34 weeks) and Late Onset of Preeclampsia (LOPE; $\geq$34 weeks) patients and for the identification potential biomarkers playing a role in aberrant placental development and to understand the pathophysiology of PE. Placental tissues were collected from three patient groups (Control [n = 30], EOPE [n = 30], and LOPE [n = 30]) and performed miRNA profiling by Illumina sequencing, downstream analysis for identification, quantification and expression profiling is done by the quantifier.pl script and miRDeep2.pl script.
Outcome measures
Sequence analysis showed novel miRNAs that were disease-specific and common among all studied groups, suggesting the underlying placental pathologies in EOPE and LOPE.
Results
The real-time PCR analysis of 3 miRNAs (miR4743-5p, miR149-5p, and miR331-5p) was done and observed differential expression in all three patient groups. miRNA4743-5p was found to be significantly expressed EOPE when compared to control and LOPE samples. Similarly, expression of miR331-5p was significant in LOPE samples as compared to other groups and the expression of miR149-5p was only observed in control group.
Conclusion
The integrative expression analysis of these 3 miRNAs (miR4743-5p, miR149-5p, and miR331-5p) have given a hope for early diagnosis of PE and associated complications in pregnant women.
Keywords
MicroRNA, Next-generation sequencing, Placenta, Preeclampsia. Disclosure of interest: None declared
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EP913

Association between circulating adiponectin levels and androgen excess in polycystic ovarian syndrome

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Background
Low adiponectin levels in polycystic ovarian syndrome (PCOS) have been largely attributed to obesity which is common among these patients. In addition, evidence also suggests that low adiponectin in PCOS may be related to androgen excess in these women. Therefore, the aim of the present study was to examine the association of adiponectin levels and androgens in women with PCOS.
Methods
A total of 60 women with PCOS who met the 2003 Rotterdam diagnostic criteria and 60 age and body mass index matched controls without PCOS were recruited. We determined anthropometric parameters, metabolic and endocrine indicators, serum adiponectin, and inflammatory markers, and statistically analyzed the results.
Results
PCOS women had significantly lower adiponectin level ($P<$ 0.01) compared to healthy women. The adiponectin level correlated inversely with body mass index (BMI), waist circumference (WC), body fat mass, tryglicerides, homeostasis model assessment HOMA IR, $AUC_{insulin}$, $AUC_{glucose}$, total testosterone, dehydroepian-drosterone sulfate (DHEAS) and free androgen index (FAI) and positively with sex hormone-binding globulin (SHBG) and high-density lipoprotein cholesterol (HDL) in the PCOS group. In multivariate logistic regression, BMI and FAI were significant independent determinants of adiponectin cut-off level of 7.7μg/ml.
Conclusions
In conclusion, our results confirm that adiponectin concentrations change according to variations of BMI in women with PCOS. They also suggest the role of androgen excess in obesity and adipose tissue dysfunction in PCOS women
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EP914

Kisspeptin Levels in Different Polycystic Ovary Syndrome (PCOS) Phenotypes

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Objective
To compare kisspeptin levels between different phenotypes of PCOS and to analyze the correlation between kisspeptin and PCOS-related hormonal and metabolic disturbances.
Patients and methods
The study included 87 women with PCOS, and a control group of 27 clinically healthy women, corresponding in age and BMI to the patients with PCOS. Circulating levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), sex-hormone binding globulin (SHBG), thyroid stimulating hormone (TSH), prolactin, fasting insulin, dehydroepiandrosterone sulfate (DHEA-S) and kisspeptin were measured.
Results
There are 4 phenotypes in women with PCOS – A (oligoanovulation, hyperandrogenism and polycystic ovaries) (n=33), B (oligoanovulation and hyperandrogensim) (n=21), C (hyperandrogenism an polycystic ovaries) (n=19) и D (oligoanovulation and polycystic ovaries) (n=15). There were no significant differences in age (P=0.615) and BMI (P=0.223) between the 4 PCOS subgroups. We found difference in terms of BMI (p = 0.003) only between phenotype A and the control group. We did not find any significant difference between the four PCOS subgroups in terms of kisspeptin, LH, FSH, LH/FSH, E2, TSH, fasting insulin, and prolactin. T levels were significantly higher in phenotype A compared to phenotype D (P=0.028), and DHEA-S was significantly higher in phenotype B compared to phenotype D (P=0.045). In the PCOS group we found a positive correlation between kisspeptin and age (r= 0.250; P= 0.019), BMI (r= 0.259; P= 0.02), FAI (r= 0.354; P= 0.001), A4 (r= 0.435; $P<$ 0.001), fasting insulin (r= 0.299; P= 0.005), and negative one with SHBG (r= -0.319; P= 0.003), DHEA-S (r= -0.282; P= 0.008), PR(r= -0.249; P= 0.020).
Conclusions
Our results indicate that kisspeptin levels are comparable between different PCOS phenotypes and with the control group. Kisspeptin might be associated with metabolic disturbances in PCOS women.
Key Words
PCOS, phenotypes, kisspeptin
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EP915

Genetic bases of hereditary gonadotropin-dependent precocious puberty

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Background
Nowadays, single nucleotide polymorphisms in genes *KISS1, KISS1R, MKRN3, DLK1* have been described as the leading cause of precocious hypothalamic-pituitary axis activation in children. Genetic testing in patients with hereditary forms of precocious puberty (PP) can expand our knowledge in underlying molecular mechanisms of the disease. The diagnosis of genetic bases is necessary for genetic counselling.
Aim
To access clinical characteristics and define genetic defects in patients with hereditary forms of gonadotropin-dependent precocious puberty.
Materials and Methods
21 patients with positive family history were enrolled into the study: 8 patients were with paternal disease history, 6 – with maternal. 7 patients had siblings with diagnosed PP. The full-exome sequencing was conducted in all the patients.
Results
The median of patients age at the time of the examination was 7,2 years [6,5; 7,7]. Single nucleotide variants were identified in 13 (62%) of patients. *MKRN3* gene defects were the most common: 10 out of 13 patients had defect in this gene. The rest of the group had defects in genes associated with neuroontogenesis and neuroendocrine regulation mechanisms of hypothalamic-pituitary axis: *MAP-K8IP3* (OMIM no. 605431), *POU1F1* (OMIM no. 173110) and *NPFF1R* (OMIM no. 607448).
Conclusion
MKRN3 defects are the most common genetic cause of hereditary forms of gonadotropin-dependent PP which is consistent with worldwide data.

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EP916

Coexistence of Turner syndrome and Rokitansky-Küster-Hauser

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Introduction
Turner syndrome (TS) is a genetic condition, that results from the complete or partial loss of the second X chromosome in phenotypic females. Typically, patients with TS have growth retardation, altered pubertal development and facial dysmorphism. It's also associated with other comorbidities.
Aim
Here we report a rather rare finding which is the association of TS and Rokitansky-Küster Hauser (RKH) and we discuss the possible ethiopathogenic links between these two congenital conditions.
Case
A 16-year-old girl was referred to the Endocrinology department at the Hedi Chaker hospital in Sfax, Tunisia, for growth retardation and delayed puberty. Sha had no particular familiar nor personal medical history. She was the offspring of a consanguineous couple. On physical examination, she had a short height of 147 cm (-2 standard deviations), a normal weight of 54 kg (10^{th} percentile). She had dysmorphic features: Pterygium Colli and cubitus valgus. She also had café au lait spots disseminated all over her body. Additionally, she had a primary amenorrhea and pubertal delay as testified by the absence of secondary sexual characteristics at the age of 16. Hormonal evaluation revealed low estradiol (10 pg/ml) associated with high levels of FSH and LH: 107 mui/ml and 31 mui/ml, respectively, confirming thus the diagnosis of primary ovarian insufficiency. The karyotype confirmed our suspicion since it unveiled the presence of X monosmy. A pelvic ultrasound was also performed and since it showed the absence of ovarian structures as well as the absence of uterus, a pelvic MRI was carried out. This latter exam confirmed the absence of ovaries and uterus. However, it showed a normal aspect of vagina and the presence of feminine urethra. These imaging findings are attributable to RKH.
Conclusion
Although rare, RKH and TS can be associated. The coexistence of these two conditions further complicates the management of infertility in patients with TS.

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EP917

Developmental neuro-toxicity evaluation of endocrine-disrupting chemical butylparaben

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Butylparaben is an endocrine disrupting chemical (EDC) which is used as antimicrobial preservative in many cosmetic products. EDCs are structurally diverse class of synthetic and natural compounds. EDCs can cause non-communicable diseases such as obesity, type 2 diabetes, and neurodevelopmental disease. Present study investigated that whether exposure to butylparaben during maternal pregnancy could cause the offspring's neuronal development disorder. *In vitro* study butyl paraben promoted apoptosis and inhibited proliferation of Sox1-GFP cell. The mRNA expressions for ER stress were evaluated. Furthermore, *in vivo* study for developmental neuro toxicity test battery for butylparaben was carried out. Butylparaben 100 mg/kg, 50 mg/kg was treated for pregnant mouse from E10.5 to weaning period. The result of behavior test shows abnormal cognitive, social and anxiety like behavior in butyl paraben treated mice. *In vitro* study, ER stress genes was evaluated, BiP, CHOP, and AFT6 were significantly up-regulated following treatment with EDC. From these results, butylparaben is a potential neuro developmental toxicant.

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EP918

Normative Range of 17-hydroxyprogesteroneamong Indian Reproductive Age Women

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Background
Non-classic adrenal hyperplasia (NCAH), comparatively a rare disease, is characterised by mild to moderate hyperandrogenemia, hirsutism, oligomenorrhea, insulin resistance which incidentally are the hallmarks of polycystic ovary syndrome (PCOS)- a common disorder among reproductive aged women. The data on 17-hydroxyprogesterone (17-OHP)serum levels in NCAH has been reported globally but there is limited data available regarding the normal range among healthy Indian reproductive age women.
Aim
We aimed to evaluate serum 17-OHP levels among healthy women of reproductive age from India as a reference range.
Materials and methods
A total of around 450women of reproductive age (18-40years) were recruited from different urban [$n=226$ (50.2%)]and rural[$n=224$ (49.8%)]regions of the country. The anthropometric, clinical and biochemical parameters were obtained using standard uniform questionnaire. The samples from all the subjects were collected during their follicular phase of menstrual cycle and assessment of 17-OHP was carried out using ELISA method (DiaMetra S.r.l., Segrate, Italy). The 95% of the reference distribution was estimated using 2.5^{th} - 97.5^{th}percentile limits.
Results
The mean $\pm$SD of age and body mass index (BMI) of participants was 30.12 $\pm$ 6.32years and 22.8 ± 3.36 kg/m^2 respectively. The age of menarche for the subjects was reported to be 13.05 ± 1.35years). The mean percentages of 17-OHP serum levels among recruited subjects were 0.49 ± 0.259ng/ml with the median of 0.49ng/ml and range between 0.0059–2.0 ng/ml. The 2.5^{th} - 97.5^{th}percentiles of 17-OHP among subjects at 2.5^{th}; 5^{th}; 10^{th}; 25^{th}; 50^{th}; 75^{th}; 90^{th}; $95^{th}$and 97.5^{th}were reported as 0.09; 0.959; 0.15; 0.30; 0.65; 0.85; 0.81; 0.85 and 1.19 respectively.

Conclusion
This study is first of its kind to collect a data from a large representative sample of reproductive age Indian women. The data will serve as a reference range among healthy women of reproductive age.

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EP919

Serum AMH in women with polycystic ovary syndrome

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Background and Aims
Anti-Müllerian hormone (AMH) is secreted by granulosa cells of ovarian follicles. Since AMH reflects the number of antral follicles and the pronounced androgen secretion from follicles/stroma in women with polycystic ovary syndrome (PCOS) remains until late reproductive age, the age related relationship between AMH in women with PCOS are of interest.
Methods
Women with PCOS (aged 15–42 years) ($n=537$) participated in the study. AMH level according to age groups were investigated. The relationships between AMH and androgenic, metabolic, hormonal and ovarian parameters were also studied. Finally, multiple regression analysis was done to evaluate determinants of serum AMH level in women with PCOS.
Results
From 537 women with PCOS, 375 patients showed clinical and/or biochemical hyperandrogenism, and the remaining 162 patients did not show. Mean serum AMH level was significantly higher in hyperandrogenic patients (10.38 ng/ml, 95% CI, 9.71 - 11.09) compared with that of non-hyperandrogenic ones (8.74 ng/ml, 95% CI 7.98 - 9.58) ($P=$ 0.004). Serum AMH levels showed no differences according to different age groups (Table 1) and remained stable throughout the ages (Figure 1). In Pearson's correlation analysis, serum AMH showed significant positive correlations with total testosterone, free testosterone, log free androgen index, androstenedione, DHEAS, LH levels, mean antral follicle number and ovarian volume. A multiple linear regression model was used to determine variables which were associated with AMH level. Age did not contribute significantly to the model. Only LH, total testosterone, and mean antral follicle number contributed significantly to serum AMH levels.
Conclusions
Serum AMH levels remained high until late reproductive age and did not show significant variation according to the age groups. Hyperandrogenic PCOS patients showed higher AMH levels than that of non-hyperandrogenic patients. LH, total testosterone, and antral follicle number were main contributors to serum AMH levels irrespective of age

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EP920

Androgen insensitivity resulting in a disorder of gonadal development 46XY

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Introduction
Androgen insensitivity syndrome (AIS) is a genetic sexual developmental disorder (DSD) inherited in an X-linked recessive mode, responsible for 30 to 70% of cases of DSD 46, XY. Androgen insensitivity can be complete (CAIS), partial (PAIS) or mild depending on the degree of receptor sensitivity to androgen stimulation
Case report
A 17-year-old female patient with a history of inguinal hernia operated in childhood who was admitted for exploration of primary amenorrhea. it presents clinically a female external genital phenotype with a male genotype. Hormonal investigations revealed high level of LH at 20.37 mui/ml, FSH at 5.88 mui/ml, high testosterone at 3.61 and low estradiol at 16pg/ml. Ultrasound and pelvic MRI showed two latero-vesical formations which could be related to male gonads. This was a complete androgen insensitivity for which a gonadectomy with estrogen-progestogen replacement therapy was made.
Discussion
CAIS is a rare entity; however, it is the most common cause of 46 XY DSD, accounting for 60% of cases. The experts recommend that a karyotype should be performed in any girl presenting an inguinal hernia. In rare cases, the diagnosis is made later in life when the patient presents an infertility or during adolescence which is the case for our patient. Ultrasound, plays an important role in the diagnosis; it confirms the absence of any uterine or ovarian structure and shows the testicles in a variable position. In our patient Ultrasound and pelvic MRI showed the absence of uterine structure with 2 laterovesical formations related to male gonads. A gonadectomy is often performed due to the risk of malignant degeneration of the ectopic testicles, followed by hormone replacement therapy
Conclusion
The diagnosis of AIS is a challenge for doctors; its management is complex and requires a multidisciplinary approach

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EP921

Effects of Low-Carbohydrate Diet vs. Mediterranean Diet on Growth Factors in Women with PCOS: A Randomized Controlled Trial

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Background
Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. Ovarian fibrosis and altered angiogenesis have been discussed as important factors in the pathogenesis of PCOS. Lifestyle modification is the first step in the treatment of PCOS. However, a specific composition of diet that should be included in a lifestyle change program has not been determined.
The aim
Of the study was to compare the effects of low-carbohydrate diet (Low-Carb) and Mediterranean diet on the growth factors in women with PCOS.
Methods
62 patients with PCOS were randomized into two groups according to the recommended diet: Low-Carb ($n=32$) and Mediterranean ($n=30$). The study protocol is described at clinicaltrials.gov (NCT05272657). Fasting serum samples were collected at baseline and after 3 months of dieting. Seven growth factors were analyzed in the serum employing Luminex®xMAP™ (Merck, Germany): epidermal growth factor (EGF), fibroblast growth factor 2 (FGF2), fms-related tyrosine kinase 3 ligand (FLT3L), platelet-derived growth factor AA (PDGF-AA), platelet-derived growth factor AB/BB (PDGF AB/BB), vascular endothelial growth factor a (VEGF-a) and transforming growth factor a (TGF-a).
Results
The Mediterranean diet decreased the levels of FLT3(medians before and after diet were 13.2 and 10.3 pg/ml respectively, $P=$ 0.002), PDGF AA (5361 and 4660 pg/ml, $P<$ 0.001), PDGF AA/BB (46328 and 44910 pg/ml, $P=0.001$), TGF-a (10.8 and 10.5 pg/ml, $P=0.021$) and VEGF-a (275 and 228 pg/ml, $P=0.008$). The low carbohydrate diet, on the contrary, increased the levels of FLT3(10.7 and 12.4 pg/ml, $P<$ 0.001), PDGF AA/BB (47465 and 48404 pg/ml, $P=0.005$) and FGF 2 (59.4 and 60.7 pg/ml, $P=0.007$). When comparing the median changes between the two diets, the difference was significant for TGF-a ($P=0.010$), FLT3($P<$ 0.001), FGF2($P=0.001$), PDGF AA and PDGF AA/BB ($P<$ 0.001).
Conclusion
The Mediterranean diet reduced the levels of growth factors FLT3L, PDGF AA, PDGF AA/BB, TGF-a, VEGF-a, while the Low-Carb diet produced no changes in TGF-a, VEGF-a, EGF, PDGF AA and increased the levels of FLT3L, PDGF AA/BB and FGF 2.

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EP922

Association of Bardet-Biedl syndrome with Differences of Sex Development and pituitary hypoplasia

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Introduction
Bardet-Biedl syndrome (BBS) is a rare autosomal recessive genetic disorder involving hypogonadism manifested by cryptorchidism, micropenis and/or delayed puberty
Observation
We report the case of a 13 year old child, who was consulted for obesity and whose physical examination showed major signs of SBB: global obesity, polydactyly, learning difficulties and visual disorders. Genital examination revealed a 1 cm genital tubercle with a single orifice and two genital swelling without palpable gonads. Biological investigations revealed hypogonadotropic hypogonadism, corticotropic insufficiency, low AMH with a non-stimulable HCG test and a 46XY male karyotype. Pelvic MRI did not show any gonads or internal genitalia but noted ectopy and malrotation of the right kidney. The diagnosis of a testicular regression syndrome is very likely in this case. At the fundus photography: presence of bilateral retinal dystrophy with high myopia. At the hypothalamohypophyseal level: a strong pituitary hypoplasia was objectified.
Discussion
BBS is a rare autosomal recessive multisystem ciliopathy. The incidence of BBS is 1 in 150,000–160,000 in Europe and North America. BBS is caused by a dysfunction of the gene coding for proteins that are implicated in the function of the primary cilia and in important signaling pathways. The core features of the syndrome include retinal degeneration, obesity, polydactyly, cognitive impairment, renal anomalies and urogenital malformations. To date, pathogenic variants in 26 genes have been shown to be involved in the molecular basis of this rare ciliopathy. To our knowledge, only one study conducted on 11 children with BBS found among them 7 cases of pituitary abnormalities, 4 of which showed hypoplasia. While no association with a testicular regression syndrome has been described. This makes our patient the first described association of these 3 pathologies.

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EP923

Response to Growth Hormone Therapy in A Patient with Williams-Beuren Syndrome

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Introduction
Williams-Beuren syndrome (WBS) is a rare neurodevelopmental disorder with distinctive facial appearance, cardiovascular anomalies, impaired somatic growth and infantile hypercalcemia. Growth retardation is a common clinical feature in patients with Williams-Beuren syndrome. We report a boy with Williams-Beuren syndrome, who was found to have growth hormone deficiency and is responding well to growth hormone therapy
Observation
The patient is a 20 years old boy with consanguineous parents, born at term but we had no idea about his birth weight. He was referred to our hospital for hyperglycemia revealing diabetes. Clinical examination revealed a growth retardation, his length was 88 cm (below the 4rd percentile; SDS) and weight was 18 kg (3rd percentile), he had typical facial features including low nasal bridge, long philtrum, prominent lips with open mouth, peri-orbital fullness. On cardiological evaluation, ECG and cardiac echography revealed a normal cardiac anatomy and function without evidence of supravalvular aortic stenosis or peripheral pulmonary artery stenosis. Calcium levels were normal. Endocrine screening yielded a low IGF-I level (19.26 ng/ml) and a high TSH level of 500 mUI/l. Prolactin levels were elevated 118 ng/ml. Cortisol levels were normal. CT of the brain revealed a pituitary hypertrophy without clearly detectable circumscribed adenoma. Bone age according to Greulich and Pyle was of 1 year 6 months Treatment with human growth hormone (hGH) was started to which our patient responded well. Now, at the age of 22 years, his height is 106 cm (he gained 18 cm) but his weight is still 19 kg. Bone age increased and TSH levels are normal under treatment (levothyroxine 75 mg).
Conclusion
It is recommended to evaluate growth hormone IGF-I axis or at least screening by IGF-I measurements in all patients with this syndrome and short stature. GH deficiency might contribute to growth failure in patients with WBS. hGH therapy shows good response in these cases

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EP924

Cytogenetic Study of Primary Ovarian Insufficiency: About 90 Cases

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Background
Primary Ovarian Insufficiency (POI) is defined as the loss of ovarian function before age 40. It is characterized by menstrual disturbance with raised gonadotropins (>25 UI/l). It can manifest as primary amenorrhea (PA) or secondary amenorrhea (SA). The causes of POI include chromosomal and genetic defects, autoimmune processes, chemotherapy, radiation, infections, and surgery. However, the etiology remains unidentified in 80% of cases referred to as idiopathic POI.
Material and Methods
We report the clinical and cytogenetic study of 90 patients diagnosed with POI, collected at the Department of Congenital and Hereditary Diseases of Charles Nicolle Hospital in Tunis (Tunisia) over a period of 7 years from January 2016 to December 2022. R-banded chromosome analysis on cultured peripheral blood lymphocytes was performed in all patients.
Results
The 90 patients were referred for PA (36/90), SA (19/90), POI (26/90), and spaniomenorrhea (9/90). Their average ages were 22.9 years (14-39 years), 22.9 years (17-36 years), 32.8 years (18-40 years), and 23.6 years (14-40 years), respectively. Hormonal assessment data reported in only 46 medical files (46/90) showed high levels of FSH (>25 UI/l) in the 46 patients. Pelvic imaging was performed for 33 patients (26 ultrasounds and 7 MRIs) and revealed anomalies in 17 patients consisting in the absence of uterus and/or vagina (4/17), non-visualized ovaries (10/17), or hypoplastic ovaries (3/17). Karyotype showed anomalies in 12 patients (13.3 %): a Turner syndrome in 8/12 patients due to monosomy X in 5/8 patients (mosaic 3/5, homogenous 2/5), mosaic Xq isochromosome in 2/8 patients, and a mosaic ring X chromosome in 1/8 patient, all of them having PA, a supernumerary marker chromosome in one patient with SA (1/12), a balanced translocation 46,X,t(X;17)(q21.3;q22) in one patient with SA (1/12) and 46,XY Karyotype in two patients with female phenotype, gonadal dysgenesis and PA(2/12).
Conclusion
These results are consistent with those reported in the literature. Indeed, in our study, chromosomal anomalies were responsible for 13.3% of POI cases vs 10-13% in the literature, the majority of which are X chromosome abnormalities. According to this high rate of chromosomal abnormalities, the karyotype must be performed for all patients with non-iatrogenic POI as recommended by the European Society of Human Reproduction and Embryology (ESHRE,2015).

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EP925

Serum AMH levels and insulin resistance in women with Hashimoto thyroiditis

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Objective
Women with Hashimoto thyroiditis (HT) could have fertility problems. Serum anti-Müllerian hormone (AMH), which reflects functional ovarian reserve, is decreased in women with HT. The aim of the present study was to investigate the relation between serum levels of AMH and insulin resistance in women with HT compared to control group.
Patients and methods
We examined 193 women: 37 subjects with HT, without previous history of treatment with L-thyroxin, and 156 control women. Serum concentrations of AMH, TSH, thyroid hormones, insulin, glucose, HbA1c, lipids were assessed. HOMA-IR was calculated.

Results
We did not observed differences in serum concentration of AMH in women with HT in comparison to the control group ($P=0.26$). We also did not noticed differences in serum levels of TSH, thyroid hormones, glucose, insulin, HOMA-IR, HbA1c and lipids between studied groups (all $P>$ 0.05). In women with HT, we observed relationships between serum levels of AMH and insulin ($r=0.34$, $P=0.03$), we also observed that AMH levels was connected with HOMA-IR ($r=0.36$, $P=0.02$) in women with HT. However, we did not find relation between serum concentration of AMH and HOMA-IR in the control group ($r=$-0.03, $P=0.68$).
Conclusions
We observed in women with HT connection between insulin resistance and marker of functional ovarian reserve.

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Growth hormone treatment in SGA children leads to worsening of insulin resistance parameters without beneficial effects on lipid profile – a 3-year retrospective study

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Background
Children who were born small for gestational age (SGA) and who do not have adequate catch-up growth until 4 years old have indication for treatment with recombinant human growth hormone (rhGH). The metabolic consequences of this treatment are relatively unknown.
Objective
To evaluate the effect of rhGH treatment on insulin sensitivity and lipid profile.
Materials and methods
A retrospective observational study of children born SGA who underwent rhGH therapy was performed. Data was assessed before treatment and yearly (three-year follow-up).
Results
A total of 25 SGA children were included. The median age of the children at rhGH treatment was 5.0 (IQR 4.0-9.0) years old. A statistical significant increase in IGF-1 was observed in all years of follow-up. Fasting plasma glucose increased during follow-up, with significant differences in first and third year. Fasting insulin and HOMA-IR values tended to increase, with significant differences observed during the second and third year. The analysis on lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides) was not statistically significant. Height (Z-score) increased significantly (basal: −3.0; first year: -2.3; second year: −2.1; third-year -2.1). The effect of rhGH treatment on stature (ΔZ-core) was not relatable with insulin resistance, lipid profile or age at beginning of treatment.
Conclusion
Fasting plasma glucose, fasting insulin and HOMA-IR increased significantly during follow-up. No significant differences were found on lipid profile. No relation was found between the effect on height and metabolic consequences.

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EP927

A Late Diagnosed Case of Charge Syndrome

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Background
CHARGE Syndrome is a rare inherited congenital disorder [1]. The name reflects the initials of the clinical findings (Coloboma, Heart disease, Atresia of the choanae, Retarded growth and mental development, Genital anomalies, Ear malformations, and hearing loss). The disease has four major findings expressed as 4C; ocular coloboma, choanal atresia, cranial nerve abnormalities, and characteristic ear anomalies [2].
Objective
Here, a case of CHARGE syndrome, which had no ocular coloboma and choanal atresia findings but had other features and was diagnosed genetically at a late age, was discussed.
Case
The 20-year-old male patient who had no problems during delivery had recurrent pneumonias. He was operated because of vascular ring compression on his esophagus. Inner and outer ear anomalies and mixed hearing loss were present. His neurological development was retarded. Block appearance was detected in the cervical vertebrae. Orchiopexy was performed at 2-3 years because of his undescended testis. Hypogonadotropic hypogonadism was found with micro genitalia. In his family history, there were consanguinity and suspicious deaths in his siblings. In physical examination, his final height was 172 cm. He had a short neck, an atypical facial appearance, prominent auricles, abnormal ears, short philtrum, low nuchal hairline, mild kyphoscoliosis, gynecomastia, and micro genitalia. Pubic and axillary hair growth was insufficient. At the age of 18, a heterozygous mutation in the *CHD7* gene (p. Gnl 171Ter) was detected in a genetic examination. Because of delayed puberty and hypogonadotropic hypogonadism, choriogonadotropin alfa was started.
Conclusion
In CHARGE syndrome, neural crest-derived organ anomalies develop due to mutations in the *CHD7* gene [1, 3]. Some of the major findings such as coloboma and choanal atresia may not be present in some cases with a genetic mutation [4]. In our case, other features of the syndrome were observed. Genetic consultation should be requested for patients with characteristic CHARGE syndrome features, even if not all major features are present.
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EP928

Postponed gonadectomy until adulthood for a patient with a novel mutation in androgen receptor gene: a case report

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Introduction
Androgen insensitivity syndrome rare X linked disorder that is typically characterized by evidence of feminization of the external genitalia at birth, abnormal secondary sexual development in puberty, and infertility in individuals with a 46,XY karyotype. Complete androgen insensitivity syndrome (CAIS) usually is recognized only at the teenage age due to primary amenorrhea. Recently, gonadectomy for patients with CAIS are postponed due to a mild risk of malignancy.
Case report
This report refers 15.3-year-old patient, assigned as female, who presents with primary amenorrhea. Physical examination observed the female appearance and normal external genitalia with a 4 cm length of vagina, puberty maturation was evaluated B4P1-2 (by Tanner stage). Laboratory examination showed high levels of testosterone and anti-Müllerian hormone, and normal levels of gonadotropins and estradiol; the uterus was absent but observed bilateral solid formations in the pelvic MRI. Chromosome analysis confirmed a 46,XY karyotype. Sanger sequencing of AR (NM_000044.6) gene from blood leukocytes DNA was performed and a novel hemizygous likely pathogenic variant c.232_241del p.(Gln78ArgfsTer94) was detected. This variant also confirmed in the testicular tissue DNA. The diagnostic laparoscopy was performed, and histological analysis of the bilateral gonads showed the immature testis tissue with Sertoli and Leydig's cells. During laparoscopy, also open processus vaginalis was found. Contralateral inguinal hernia was operated on in infant age. The CAIS was

confirmed. Gender was assigned as female, but gonadectomy was postponed and hormonal therapy by estrogen did not initiate due to normal level of estrogen and bone mineral density (BMD).
Conclusions
Historically, the gonadectomy for individuals with CAIS was performed after conforming diagnosis at various ages to avert the risk of gonadal malignancy. Recently, gonadectomy is postponed until early adulthood age (25–30 y.o.). Postponed gonadectomy prevents postsurgical hypogonadism which might have negative effects on cardiovascular health and BMD [1].
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EP929

Turner patient with positive SRY gene: Case report

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Introduction
Many studies demonstrated that 40%-60% of Turner patients were 45,X monosomy in blood lymphocytes, whereas the remaining patients had a structurally abnormal X- or Y-chromosome or were mosaics with a second cell line containing a normal or an abnormal sex chromosome.
Case Summary
Five years old girl was brought to pediatric clinic for short stature. On exam, her height was 92 cm (<3th percentile), body weight was 13.3 kg (<3th percentile). She had neither cubitus valgus deformity nor webbed neck. Knuckle sign was negative. Audiometry, echocardiography, kidney ultrasonography were all immature. Her karyotyping revealed 45,X and FISH analysis indicated that the *SRY* gene was positive. After diagnosis of Turner syndrome, growth hormone had been given for the treatment of short stature. At the age of fifteen, her height was 149 cm (+2 SD) and her body weight was 68 kg (>97th percentile). Estradiol replacement was started at the age of 15 years and 10 months. On pelvic echography, the uterus and both fallopian tubes looked immature, but both gonads looked streak in appearance. Because SRY gene was positive, exploratory laparoscopy was indicated for prophylactic removal of dysgenetic gonads.
Conclusion
It is recommended that individuals with Turner syndrome be screened for Y chromatin. Detection of this will provide information and guidance to individuals with Turner syndrome, especially in terms of the risk of developing gonadoblastoma, with advanced clinical consultation.

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EP930

Clinical characteristics of men with primary hypogonadism in late-onset hypogonadism

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Late-onset hypogonadism (LOH) remains a debatable entity in terms of diagnosis and management. However, the finding of primary hypogonadism (PHG) in ageing men, in the absence of organic cause, provides an unequivocal biochemical diagnosis. Indeed, it has been established in European Male Ageing Study (EMAS) that PHG, and not secondary hypogonadism, is strongly associated with advanced age and multi-comorbidities. That would be consistent with the underlying pathophysiology of Leydig cell dysfunction occurring with ageing process. PHG in ageing men (LOH-PHG) is a relatively rare disorder, affecting only 2.7% (54/1991) of the EMAS baseline cohort (after exclusions). Some of the associated clinical features described were decreased sexual function, lower haemoglobin level and increased insulin resistance. In the current report, baseline clinical characteristics of ten middle-aged to older men diagnosed with LOH-PHG are described. This is a single centre study based on the experience of a specialised Men's Health clinic under the Endocrinology service in Singapore General Hospital. Men with a T <10.5 nmol/l and a LH >9.4 U/l were considered to have PHG. Patients were self-referred, or referred from either primary care or other specialities for suspicion of low testosterone. Mean age of diagnosis of hypogonadism was 66 years (range 55-77). All men had 3 or more co-morbidities. Baseline prevalence of common chronic conditions is as follow – Overweight (BMI > 25 kg/m2): 80%, Diabetes mellitus: 50%, Hypertension: 80%, Hyperlipidaemia: 100%, Coronary artery disease: 50%, Cerebrovascular disease: 20%, Chronic kidney disease: 40%, Osteoarthritis of knee: 20%, Parkinson disease: 10%. At diagnosis, the mean Follicle Stimulating Hormone (FSH) and Luteinising Hormone (LH) levels were 44.3 ± 15.0 IU/l and 22.8 ± 8.5 IU/l respectively, while the mean total Testosterone (T) level was 5.9 ±1.9 nmol/l. Eight men had a haematocrit of <43%; the other two had 46.1% and 48.7%. The mean PSA level was 2.0 ± 1.8; one individual with an elevated PSA had a normal prostate biopsy subsequently. All men were symptomatic at presentation. Besides erectile dysfunction (70%), the chief presenting complaints were mostly related to loss of muscle strength and energy (60%), reflecting the concern of loss of physical function. Three patients had distressing vasomotor symptoms including hot flushes and sweating accompanied by mood swings, poor concentration and impaired sleep quality, with one of them being treated for mood disorder prior to diagnosis of LOH. Interestingly, spironolactone-induced gynaecomastia was the primary indication for hormonal evaluation in two men.

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Clinico-biological and etiological analysis of patients followed for hirsutism

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Introduction
Hirsutism is defined as excessive pilosity development in women in androgen-dependent areas. It is the main revealing sign of hyperandrogenism. It is a frequent reason for consultation in Endocrinology.
Methods
This is a retrospective study of 82 records of patients hospitalized for exploration of hirsutism in the endocrinology department of Farhat Hached Hospital in Sousse, over a period of 20 years from 1997 to 2017.
Results
The mean age of the patients was 25 years, with extremes of 16 to 38 years. Family history included hirsutism in 41%, diabetes in 29%, hypertension in 22%, and obesity in 13%. Among the patients, 18% were diabetic, with a single case of type 1 diabetes, and 14% were hypertensive. Menstrual disorders such as spaniomenorrhea were observed in 70% of the cases, 23% had secondary amenorrhea. Primary infertility had been found in 6% of cases. Hirsutism appeared in the pubertal period in 40% of cases and in the post-pubertal period in 60% of cases. The major site of hirsutism was the face in 53% of patients. Assessment of hirsutism by the Ferriman-Gallway score showed mild hirsutism in 30% of cases, moderate in 44% of cases and severe presentation in 26% of cases. Overweight had been observed in 42% of the cases, 30% were obese, while 30% of the patients were at normal range. An android distribution of obesity was found in 25% of cases. Acanthosis nigricans was present in 17% of cases, Cushing's syndrome in 10% and signs of virilization in 3.6%. Biological investigations showed an increase in total testosterone level in 84% of cases. The etiologies found were: polycystic ovary syndrome (PCOS) in 60% of the cases, idiopathic hirsutism in 20% of the cases, Cushing's syndrome in 11% of the cases (5 cases of Cushing's disease and 4 cases of cyclic Cushing's disease), congenital adrenal hyperplasia by 21-hydroxylase deficiency with a late onset in 5% of the cases, and hyperprolactinemia in 4% of the cases.
Conclusion
PCOS is the most common etiology of hirsutism, which develops progressively with a peripubertal onset. However, a careful etiologic investigation is always necessary in order not to miss an ovarian or adrenal virilizing tumor origin in case of recent and rapidly evolving hirsutism.

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EP932

Multisystemic maccune albright syndrome: what is the management

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Introduction
Maccune albright syndrome; is a rare disorder resulting from the involvement of several organs; the phenotype is variable depending on the clinical manifestations linked to the importance of the tissues affected by the mutation.

Case report
In our patient, the diagnosis was not made until she was 8 years old, despite some suggestive signs: as café au lait skin macules at birth and early forearm bone fractures at the age of 3 years. At 8 years; she presents all the manifestations of the syndrome:
- peripheral precocious puberty: the patient is classified as S3 P3 and the mother reports 2 episodes of vaginal bleeding Hormonal assessment shows an elevated oestradiol level of 326 pg/ml with suppressed FSH and LH. Ultrasound of the internal genitalia shows a pubere uterus with cysts.
- multiple polyostotic fibrous dysplasia disease: Technetium-99 scintigraphy scan showing increased tracer uptake in areas of fibrous dysplasia, including the skull, spine, humerus, costal grill distal third of the right ulna spine and sacroiliac bones.
- Peripheral FT3 hyperthyroidism: thyroid ultrasound revealed an enlarged thyroid with multiple cystic anechoic formations in both lobes
Discussion
Management of Mccune Albright syndrome is cumbersome; diagnosis is often unrecognised; late in our patient, but there is no doubt about the diagnosis. Our patient has a combination of bone, skin, gonadal and thyroid involvement. In order to detect and identify occult bone damage, we performed a bone scan, which revealed multiple damage justifying a complete clinical and radiological assessment and rigorous monitoring. The patient does not have disabling bone pain that warrants biphosphonate treatment. The height obtained after treatment with androcur and synthetic antithyroid drugs is acceptable: the patient has a height of 165 mm; Radical treatment of hyperthyroidism will be discussed with a preference for total thyroidectomy.
Conclusion
Maccune Albright Syndrome is rare but the management of these children is quite heavy and continues into adulthood. In our patient, despite a multi-systemic form, the target size is correct; there are no deformities or major fractures and no functional impotence, despite the delay in diagnosis Monitoring of these patients continues throughout their lives as the disease remains active and requires multidisciplinary management in order to watch out for any complications or sarcomatous or mammary transformation

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Ovarian steroid cell tumor – a rare cause of androgen excess in a young woman

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Introduction
Signs of hyperandrogenism are frequent complaints for young adults and adolescents and a common cause of presentation to endocrinology service. Even if polycystic ovary syndrome is the most frequent etiology, differential diagnosis is mandatory. (1,2)
Case report
We present the case of a 26-year-old female patient, obese, smoker, with a personal history of polycystic ovary syndrome and a family history of diabetes mellitus, who presented to our endocrinology clinic for the investigation of secondary amenorrhea and recently installed hirsutism. Clinically, the patient presents menstrual irregularity (last menstrual cycle 8-9 month ago), hirsutism (Ferriman Gallwey score 16) and acne; BMI 32.05 kg/m^2. Biological assessment revealed hyperandrogenism (testosterone 263,5 ng/dl, androstenedione 20,347 ng/ml and 17-OH-Progesterone 29,361 nmol/l) while normal gonadotropins levels, presence of insulin-resistance (HOMA-IR 3,7) and normal values of DHEAS, Prolactin, Estradiol, beta-HCG, inhibin. Cortisol hypersecretion/insufficiency was excluded and the thyroid function was normal. Transvaginal ultrasound identified the left ovary transformed into a tumor mass, inhomogeneous, hyperechoic, well-defined, well vascularised, measuring 4.4/4.2/4.8 cm. Laparoscopic excision of the tumor was performed. Histopathological and immunohistochemical examination confirmed a benign ovarian steroid cell tumor (NOS), with lipid rich cytoplasm (mitotic index 2/10< HPF, Ki67 4%, diffuse positivity for inhibin, calretinin and focal positivity for Melan A). Postoperatively, androgens values ameliorated - testosterone and androstenedione normalized (29,10ng/dl and 1,8ng/ml), 17-OH-Progesterone decreased but still mildly high (7,575nmol/l), the rest of the blood results being normal and clinically - menstrual cycles regulated without significant hirsutism amelioration and the patient lost weight (BMI 29,9 kg/m^2).
Conclusion
Ovarian steroid cell tumours NOS, even if are rare, should be considered in any case of hyperandrogenism and excluded if elevated androgens levels are present. We identified a rare cause of hyperandrogenism in this patient even though many other causes were possible. Due to the fact that our patient wants to remain pregnant, it was decided to perform only the resection of the tumor, with the preservation of ovarian tissue.
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EP934

Assessment of metabolic control indicators in women of reproductive age with polycystic ovarian syndrome

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The objective is to assess the presence of possible correlation between the calculated body fat percentage (BFP) indicator and indicators of metabolic control in women of reproductive age with polycystic ovarian syndrome (PCOS).
Materials and Methods
The study included 80 women with a diagnosed PCOS according to the Rotterdam criteria. All study participants underwent standard general clinical studies with the determination of body mass index (BMI), waist circumference (WC) and laboratory tests (total cholesterol (TC), high density lipoproteins (HDL), non-HDcholesterol (non-HDcholesterol), glycated hemoglobin (Hb1c), C-peptide and insulin). The Visceral Obesity Index (VOI) and BFP were calculated. Mathematical analysis was carried out using the Statistica 10 program (StatSoft, USA). Differences were considered statistically significant at $P < 0.05$.
Results and Discussion
The results of the anthropometric study showed that the median BMI was 25.00 [20.00;29.50] kg/m2, the median WC was 85.00[69.00;90.00] cm, the median VOI was 0.79 [0.39; 1.46], BFP 30.35 [24.60 35.98]. Pro-inflammatory biomarkers were assessed, as median CRP was 0.83[0.44;2.12] mg/l, median fibrinogen was 3.70 [2.90;4.40]g/l. When assessing the state of lipid metabolism, it was found that the median values of blood lipid spectrum indicators were: TC 4.54[4.00; 4.92] mmol/l., HD1.57[1.28; 2.11] mmol/l, non-HDcholesterol 2.78[2.40; 3.52] mmol/l. Median Hb1c was 4.90[4.60;5.20] %, insulin 11.00[5.50;15.90]ng/ml, C-peptide 2.05[1.28; 2.84]ng/ml. Based on the results of the correlation analysis, a significant direct relationship was determined between the BFP and the VOI value ($r=0.75$; $P < 0.05$), WC ($r=0.88$; $P < 0.05$), insulin level ($r=0, 56$; $P < 0.05$), C-peptide level ($r=0.59$; $P < 0.05$), non-HDcholesterol value ($r=0.60$; $P < 0.05$), CRP level ($r=0.78$; $P < 0.05$). Correlation between BFP and the Hb1c level ($r=0.09$; $P > 0.05$), fibrinogen ($r=0.45$; $P > 0.05$) was not noted.
Conclusion
Estimated indicator of BFP is directly correlated with indicators of carbohydrate and fat metabolism in women of reproductive age with polycystic ovarian syndrome.

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EP935

Testosterone therapy in chronic liver disease

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Background
Several clinical features of chronic liver disease, such as sarcopenia, anaemia, low bone mass and gynecomastia are similar as manifestation of hypogonadism. Decreased testosterone levels are common in patients with severe liver disease and are associated with worse clinical outcomes and mortality.
Case Presentation
A 33-year-old patient was admitted to the hospital due to severe alcoholic hepatitis. He was in poor general condition, icteric, encephalopathic with

peripheral edema and mild ascites. Due to high Maddrey score, corticosteroid therapy was initiated, leading to a gradual decrease in bilirubin and liver enzymes but his clinical condition remained poor. The patient lost 23 kg of body mass within 2 months and his body mass index (BMI) was 21 kg/m2. The SARC-F score (Strength-Assistance walking-Rice from a chair-Climb Stairs-Falls) was 4. Laboratory findings suggested hypogonadotropic hypogonadism (LH 1.92 IU/l, FSH 1.65 IU/l) with very low free testosterone levels (32 pmol/l, ref. range 170 - 660) corrected for albumin and SHBG. Transdermal therapy with 25 mg/day of testosterone gel was initiated. Liver enzymes were slightly elevated (< 1.5 ULN) at the time of administration of testosteron and glucocorticoid therapy was discontinued. A month later, free testosterone was 151 pmol/l and there was a clinical increase in muscle strength and mobility. Dose of 50 mg/day was continued. Body mass further increased (BMI 24 kg/m2); the patient became fully independent in performing physical tasks while free testosterone reached normal levels (251 pmol/l). Liver parameters improved and no side effects occurred. We decided to continue testosterone therapy until further recovery of liver function.
Conclusion
Due to high incidence of hypogonadism, testosterone levels should be assessed in younger patients with severe liver diseases. The transdermal administration of testosterone therapy avoids hepatic circulation and prevents potential occurrence of hepatotoxic effects. It dramatically improved frailty in our patient and similar results have already been described, but this therapeutic option is still not widely prescribed. Further research on long term risk and benefits of transdermal testosterone therapy in chronic liver diseases is required.

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EP936

Treatment Challenges of a virilized female with 46 XX CAH diagnosed at the age of 13

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Introduction
DSD is a group of disorders by which there is discrepancy between genomic sex and phenotypical sex. Most of cases of DSD are picked up during neonatal period due to ambiguous genitalia. Few cases are diagnosed in adolescence or even at puberty due to various causes like mild ambiguity, complete phenotype sex reversal, lack of breast development and primary amenorrhea, we review a case of 46XX CAH girl due to CYP21 hydroxylase deficiency which was diagnosed late at the age of 13 and the implication of late diagnosis on disease control, mental and sexual aspects.
Methods
13-year-old female presented with progressive features of virilization started at the age of 10 including deepening of the voice, muscular features, severe hirsutism modified Ferriman-Gallwey Score 4, absence of breast, balding, ambiguous genitalia (grade 2 Prader) She is a daughter of consanguineous marriage. She has no depressive symptoms and perceive her self as a female but she is sexually attracted to females.
Labs
Diagnosis of 21 hydroxylase deficiency (simple virilizing form) with no features of cortisol deficiency, we started steroid replacement as hydrocortisone. No satisfactory response clinically to steroid after 6 months of treatment, patient gained weight so decided to stop medication and lost to follow up, she came again 2 years later but she refused steroid so I started potent anti androgen (Flutamide)250 mg once daily Plus COC, withdrawal bleeding occurred after 3 cycles, mild improvement in Hirsutism and psychological wellbeing after 6 months of treatment. However, her sex orientation didn't change raising the question about the impact of long exposure of the brain to androgens and highlight the concept of brain virilization.

Hb	16	%
S.K	3.9	145
S, Na		
Meq Testosterone	3.5	ng/ml
	12	nmol/l
LH	0.5	i.u.
FSH	4.5	i.u.
DHEAS	More than 1000	mg
ACTH	450 pg	
Cortisol	450	nmol
Basal17-OH progesterone	12000	ng/dl
	360	nmol
Estradiol	126	Pg
Karyotype	XX	
CT	Negative for tumor, diffuse bilateral enlargement	
Pelvic imaging	Normal sized uterus and ovaries	
Renin	1.4	ng/ml/hr

Conclusion
Current available therapies of CAH have limitations and difficult to balance the hyperandrogenism hypercortisolism arms, the effect of long-term exposure of the brain to androgens should be widely investigated in terms of gender identity, gender role and sex orientation and whether the available therapies address or reverse these issues.

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EP937

Preventing female virilisation: role of antenatal dexamethasone

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Introduction
Antenatal treatment with dexamethasone in pregnancies affected by congenital adrenal hyperplasias (CAH) therefore suppresses fetal androgen production and prevents virilisation of female infants. Antenatal DXM is reported to be efficacious, preventing or ameliorating virilisation in 80–85% of cases.
Case report
23-year-old patient pregnant at 6 weeks, not known of having congenital adrenal hyperplasia (CAH), concept of consanguineous marriage 1 degree; she had a history of 2 children followed up for a classic form of HCS, the first died at the age of 1 and 10 months and the 2 child died on D26 of life. After having made a prenatal diagnosis where an analysis of the SRY gene on fetal circulating DNA showed the absence of this gene, which confirms the female sex of the fetus. An obstetrical ultrasound was done which objectified a pregnancy estimated at 6 weeks with suspicion of clitoral hypertrophy (At 16 weeks), in view of this observation the patient was referred to us for additional care and possible dexametasone. On questioning, the patient did not report any signs of hyperandrogenism. All evolving in a context of unquantified moderate weight loss and asthenia without signs of adrenal insufficiency. The clinical examination showed no melanoderma or slate spots, BP= 105/71mmHg, RR = 19 cycles/min. CF=81bpm? BMI = 28.68 kg/m2. Tanner: S5P5. the patient was put on 1.5 mg/d of dexamethasone divided into 3 doses. A monthly measurement of DHEAS and cortisol was requested. The Decrease of plasma concentrations of cortisol and DHEAS in the mother testifies to good fetal adrenal suppression. A low-calorie diet and monitoring of blood pressure and blood sugar to detect signs of under or overdose of corticosteroid therapy. Ultrasound monitoring of the fetus done each month, the first ultrasound done 1 month after Dexamethasone treatment shows the disappearance of the clitoral hypertrophy seen on the initial ultrasound. patient gave birth at 38 weeks of amenorrhea by caesarean section, the newborn is female, the birth weight is 2 Kg 600, the external genitalia are normal The newborn was hospitalized in the neonatology department for monitoring and screening of The congenital adrenal hyperplasia.
Conclusion
CAH is an uncommon but important and ethically complex condition where there are significant maternal and fetal risks both with and without antenatal treatment. It is time for the historical recommendation of administering prenatal DXM to all pregnancies of high-risk families for CAH to be reevaluated.

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EP938

A case of Leydig cell tumor in an adult patient with Klinefelter syndrome

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Introduction
Leydig cell tumor is rare, accounting for 1% of testicular tumors. Klinefelter syndrome is most often associated with extra-gonadal germ cell tumors. Its association with testicular tumors remains less frequent. Herein, we report the case of a Leydig cell tumor of the testis in a patient with Klinefelter syndrome.
Observation
A 46-year-old man was referred to our department for hypogonadism. His past medical history included type 2 diabetes. He presented with erectile dysfunction and decreased libido. On physical examination, he had a body weight of 96.5 kg, a height of 175 cm, a body mass index of 31.5 kg/m^2, no gynecomastia, decreased pubic hair, hypotrophic soft testicles with a hard left nodule, and a penis length of 6.5 cm. Biological investigations showed hypergonadotropic hypogonadism.

Estradiol level and tumor markers were normal. Semen analysis showed azoospermia. The karyotype showed a chromosomal formula of 47.XXY. Testicular ultrasound showed bilateral testicular atrophy with a left testicular nodule measuring 9.4×7.4 mm. The patient underwent a left orchidectomy and the histological examination concluded to a benign Leydig cell tumor.
Conclusion
The physiopathology of Leydig cell tumor remains unclear. It is suggested that the elevation of LH in patients with Klinefelter syndrome induces Leydig cell hyperplasia and tumor development. Orchidectomy represents the golden standard therapeutic option. After surgery, a long-term follow-up is indicated to exclude recurrence or metastasis.

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EP939

An Intellectual Development Disorder Revealing A Rare Variant of the Klinefelter Syndrome – 48, XXXY: A Case Report

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Introduction
Klinefelter syndrome is a sex chromosomal aneuploidy caused by an addition of X chromosome in males (47,XXY). 48,XXXY is a rare variant of this syndrome which is characterised by the presence of two additional X chromosomes in males and is estimated to occur in 1/50 000 male births. Here we describe a rare case of a 48, XXXY Klinefelter's variant in a 17 years old patient revealed by an intellectuel development delay.
Case Report
The patient was a 17 years old male, born to non-consanguinous parents after full term normal delivery. He was undergoing psychotherapy for intellectuel development delay and referred to our department for etiologic research. Clinical examination revealed a normal facial morphology with a tall stature; the presence of a delayed puberty and a micropenis are the significant features observed in the present case. The hormonal assessment was in favor of a hypergonadotropic hypogonadism profil. The cytogenetic analysis revelealed a variant of klinefelter syndrome: 48,XXXY.
Discussion
The presence of one or more additional X chromosome(s) above the typical 46,XY in males leads to testicular dysgenesis and hypergonadotropic hypogonadism, and thus, 48,XXXY is often considered a variant of Klinefelter syndrome (47,XXY) because of these shared features. However, patients with this variant have an increased risk of congenital malformations, additional medical problems, more complex psychological involvement and thus a more severe prognosis compared to patients with 47,XXY The intellectuel problem in our patient indicate the effect of the two extra X chromosomes, wherein each extra X is associated with an IQ decrease of approximately 15-16 points. Early confirmation of the diagnosis is essential for therapeutic management and genetic counselling.
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EP940

Testicular Regression Syndrome: A Case Report

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Introduction
Testicular regression syndrome is defined as partial or complete absence of testicular tissue in the presence of a normal 46,XY male karyotype. This syndrome is very rare with an estimated prevalence of 1 case/20.000 males. Here we decribe a case of a testicular regression syndrome in an 18 years old patient.
Case Report
We report the case of an 18 years old male patient followed for testicular regression syndrome since the age of 2, which was diagnosed by: The absence of palpable gonads with micropenis on the clinical examination, the absence of testicles in normal or ectopic position on the abdominopelvic and scrotal ultrasound, the hypergonadotropic hypogonadism profil, a 46,XY karyotype and the presence, at laparoscopy, of an inguinal testicle without spermatic cord measuring 13 mm on the right side and a cystic formation with a 3x7 mm tissue margin on the left one. The patient was put on androgen substitution therapy, with currently a good clinical evolution: penis with a normal size with grade 5 pilosity. Testicular prostheses with psychological support are planned.
Discussion
Testicular regression syndrome (TRS) is defined by a complete or parteil absence of tescticular tissue which may be uni- or bilateral. TRS is more common on the left side and is usually accompanied by a closed internal ring and compensatory hyperplasia of the controlateral testis. This syndrome is also known as vanishing testis, and presents clinically as nonpalpable testis. The phenotype is variable depending on the period when the gonadal regression occurs in utero. Indeed, in the presence of normal male external genitalia, it can be assumed that the fetal testis was present and functional during the early period of development with sufficient androgen production to ensure normal or subnormal male external genitalia development. In this condition, gonadal regression occurred late in fetal life, beyond the 12th week of pregnancy. However, in the presence of a micropenis, as in the case of our patient, some authors have suggested the prior presence of an intrinsic alteration of the testicular tissue before its regression.
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EP941

Case report - Charge syndrome, a rare entity in the differential diagnosis of primary amenorrhea

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Primary amenorrhea is characterized by the absence of menstruation after the age of 14 without the development of secondary sexual characteristics or after the age of 16 with the development of these. Hypogonadotropic hypogonadism (HH) corresponds to an uncommon etiology of primary amenorrhea. In HH, the differential diagnosis includes Kallmann Syndrome, isolated hypogonadotropic hypogonadism and CHARGE Syndrome. The CHARGE syndrome corresponds to an extremely rare syndrome, with an incidence of 0.1-1.2/10 000 characterized by the classic association of **C**oloboma, congenital **H**eart disease, choanal **A**tresia, **R**etardation in growth and/or development, **G**enital anomalies and anomalies from the **E**ar. It is an autosomal dominant disease, although most cases are sporadic due to de novo mutations. The exact pathophysiological mechanism of the disease is not known, but it seems to result from abnormalities of brain differentiation, namely in the migration of GnRH neurons. The CHD7 gene is the only known gene associated with CHARGE syndrome, being mutated in 75-95% of patients who meet clinical criteria for the typical form of the disease. We present the Clinical case of a patient with the diagnosis of CHARGE Syndrome since the 1st year of age, referred to an endocrinology consultation due to primary amenorrhea. Adolescent, 15 years old, CHARGE syndrome with bilateral coloboma, patent ductus arteriosus, undergoing heart surgery at age 2, profound sensorineural deafness, attention deficit disorder with autism spectrum disorder, chronic kidney disease and obesity. On physical examination Tanner stage 2 (breast 1, pubic hair 3, axillary hair 1), otherwise asymptomatic. Analytically with hypogonadotropic hypogonadism (FSH 0.4 mIU/ml, LH <0.1 mUI/ml, 17-ßeta Estradiol <19.0 pg/ml), remaining pituitary function unchanged. Gynaecological ultrasound showed prepubertal uterine morphology, with a medium-sized uterus, smaller in size for the age group, measuring 29 x 7 x 14 mm. The patient was started on 20 mg ethinyl estradiol + 150 mg desogestrel. Withdrawal bleeding was present 2 months after starting therapy. With the aim of inducing the expected gradual pubertal maturation and reducing the risk of osteoporosis/cardiovascular disease, except in cases where there is an absolute contraindication, young women with primary amenorrhea and incomplete sexual development should start estrogen therapy. We submit this Clinical case given the rarity of the entity and its importance in the differential diagnosis of primary amenorrhea.

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EP942

Correlation between metabolic and hormonal parameters in PCOS

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Introduction
Polycystic ovary syndrome is a very heterogeneous disease. Clinical and para clinical findings in such patients varies from one patient to another.
Aim
The aim of our work is to study the clinical and para clinical profile of PCOS.
Methods
This is a retrospective descriptive study of patients with PCOS followed in the endocrinology department of Hedi Chaker University Hospital of Sfax, Tunisia. PCOS + was diagnosed based on the Rotterdam Consensus definition.
Results
We collected 50 patients. The average age was 24.56 years +/- 6, 5. Subfertility was objectified in 64.7%. Family history of PCOS was reported in 10% of cases. The mean BP was 120/100 mmHg. The mean body mass index was 32.39 +/- 8.93, this could be related to the lack of physical activity (2% were actif). Despite that, only 7 women were obese. Hirsutism was noted in 85% of cases. However, the average of testosterone was at 0,66. Mean FSH, LH and estrogen levels were respectively 5.16, 10 and 52, 62 UI/ml. We have noted that 38 patients had spaniomenorrhea. Microcystic ovaries were reported in 68% of cases. The lipid balance total cholesterol levels varied between 3.22 mmol/l and 12.41mmol/l with an average of 5.12 mmol/l. We have also recorded blood sugar levels in the average of 5.6 mmol/l with a glycated hemoglobin at 5.9 % and mean insulinemia at 12,38 UI/ml.
Discussion
Until today, no consensus for the management of PCOS. Thus, a better understanding of the PCOS is necessary for a structured and well codified management. A study on a larger number of patients is recommended to better study the variability of the clinical and paraclinical profile of PCOS.

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EP943

Correlation between metabolic and hormonal parameters in PCOS

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Introduction
Polycystic ovary syndrome is a pathology increasingly observed in women of childbearing age, in whom changes in hormonal and metabolic balance have been recorded
Aim
The aim of our work is to find Correlations between metabolic and hormonal parameters in PCOS patients
Methods
This is a retrospective descriptive and analytic study of patients with PCOS followed in the endocrinology department of Hedi Chaker University Hospital of Sfax, Tunisia between 2010 and 2022
Results
50 patients were included. Mean age was 24 ± 6, 5 years. PCOS has been diagnosed at the age of 22, 5 ± 6, 17 years on average. Diabetes was found in 22% of cases overall, dysthyroidism was found in 24% of cases. However, 4% of patients were dyslipidemic. Obesity was noted in 14% of patients and 4% presented a cardiovascular event.12 women of 32 (37%) have metabolic syndrome. Prolactin was inversely correlated with LDlevel (r=-0,444). No correlation was found between HBA1C and testosterone (r= -0,277, P=0, 54). HBA1C was correlated with estrogen levels(r=0, 85, P= 0, 05). Fasting blood sugar was not correlated with FSH levels (r= -3,57, P= 0,62). The same goes for the correlation between cholesterol and estrogen levels (r=-1,04, P= 0,57).
Conclusion
This study showed a very probable relationship between metabolic and hormonal parameters. Taking these relationships into account is essential in the care of our patients.

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EP944

Late-discovered mosaic Klinefelter syndrome with severe osteoporosis and obesity

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Background
Bone mineral density measurement sometimes reveals osteoporosis that is a consequence of undiagnosed or neglected long-standing health disorders. These secondary causes of osteoporosis should be carefully investigated, especially in men.
Case Presentation
A 63-year-old male complained of back pain and was referred to endocrinology clinic due to a poor densitometry finding indicating osteoporosis. He presented with severe obesity (body mass index 40.5 kg/m^2), grade IV gynecomastia, Tanner IV genital appearance with descended testes. A spine X-ray detected compressive osteoporotic fractures in four thoracic vertebrae (Genant's grade 1 and 2). Laboratory results showed overt hypergonadotropic hypogonadism, mild normocytic anemia, vitamin D deficiency with plasma glucose and HbA1c in the prediabetes range. Peripheral blood cytogenetic analysis revealed mosaic form of Klinefelter syndrome 47,XXY/46,XY - 19 out of 21 metaphases had XXY trisomy. The patient has been married with no children and has never engaged in infertility evaluation. He had no interest in testosterone treatment for sexual dysfunction and focused only on preventing skeletal difficulties. Severe osteoporosis was treated with teriparatide for two years, followed by risedronate. His lumbar pain improved and no new fractures occurred. During follow-up his hypertension was poorly controlled and he developed diabetes, but declined bariatric surgery.
Conclusions
Bone and metabolic complications in patients with Klinefelter syndrome are mainly related to testosterone deficiency. However, testosterone replacement has not yet been approved for osteoporosis treatment due to lack of evidence that it reduces fracture risk. The benefits of testosterone on cardiometabolic disorders were found, but it is necessary to weigh them against potential risks of this therapy in older patients with established comorbidities. Although effective control of male hypogonadism symptoms is usually reported, patients with Klinefelter syndrome might exhibit psychological, cognitive, and social issues that interfere with timely diagnosis, their preference for masculinization and adoption of a healthy lifestyle.

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EP945

Down syndrome: Experience of the medical genetics laboratory of Ibn Rochd University Hospital of Casablanca

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Trisomy 21 or Down syndrome is the most common autosomal aneuploidy and the leading genetic cause of intellectual disability worldwide. It is a genetic disease, resulting from the presence of a supernumerary chromosome for the 21st chromosomal pair. It is responsible for a phenotype associating a dysmorphic syndrome, malformations (cardiac, digestive, urinary...), psychomotor retardation, and can be accompanied by other pathologies and complications (epilepsy, leukemia...). We report here the results of a retrospective study conducted at the Medical Genetics Department of the Ibn Rochd University Hospital in Casablanca, from January 2003 to December 2018, with the aim of studying the clinical and cytogenetic aspects of trisomy 21, assessing the risk factors, and highlighting the role of genetic counseling and medical and paramedical management of this syndrome. The study identified 262 cases followed for suspected trisomy 21. Among these 262 cases, we retained 64 patients with trisomy 21 confirmed by standard karyotype. The ratio was 3 boys to 4 girls. The average age at diagnosis was 4 years and 7 months. The average age of the mothers giving birth to these patients was 32.54 years. The major clinical signs in the study population were facial dysmorphia, cardiac abnormalities, hypotonia, psychomotor retardation and intellectual disability. Karyotype results showed that 92.19% of the patients had free and homogeneous trisomy21, 6.25% had mosaic trisomy, and 1.56% had unbalanced translocation. Early and multidisciplinary care by health professionals is essential to improve the quality of life of the trisomic 21 child and his or her family. On the other hand, genetic counselling must be systematic, in order to calculate the risk of recurrence, and to propose a possible prenatal diagnosis.
Key words
Trisomy 21, genetic counseling, prenatal diagnosis.

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EP946

46 xy disorders of sex development (dsd): a case report

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Introduction
Sexual differentiation depends on a succession of events, each stage of which may be the site of abnormalities resulting in sexual ambiguitý.
Case report
17-year-old female patient, consults for primary amenorrhea. On physical examination the morphotype is female, height is normal, secondary sexual characteristics are Tanner stage 1 with sexual ambiguitý Prader stage 4, No palpable testes with a subpenile Orifice. Pelvic ultrasound showed the presence of small bilateral oval subvesical images seat of small cystic areas that may be related to seminal vesicles, absence of images suggestive of uterus or ovaries. pelvic MRI showed images compatible with prostate, seminal vesicles and aplastic penis. Hormonal exploration showed hypergonadotropic hypogonadism, testosterone was 3ng/dl, and the karyotype was male, allowing us to make the diagnosis of a pure XY ADS 46. Concerning the therapeutic management, the patient will benefit from a gonadectomy with a vaginoplasty.
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EP947

Edwards' syndrome: Study of a case series
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Trisomy 18, or Edwards syndrome, is a chromosomal disorder, due to the presence of a supernumerary chromosome 18. Worldwide, it is estimated to have a prevalence of 1/6000 live births, of which the most affected are female. Infants with trisomy 18 have a high mortality rate, secondary to the lethal malformations associated with this syndrome. The objective of this study is to describe the clinical and cytogenetic characteristics of these patients and to demonstrate the value of genetic counseling. This is a cross-sectional descriptive study conducted over a period of 5 years, from July 2015 to April 2019, at the medical genetics department of the University Hospital of Ibn Rochd in Casablanca. Five patients with Edwards syndrome were admitted to the department, with a female predominance; 3 girls and 2 boys (sex ratio = 0.67). The mean age at diagnosis was 37.40 $\pm$ 23.98 days (9 days-2 months). Trisomy 18 was clinically suggested in two cases because of facial dysmorphia and malformative syndrome characteristic of the chromosomal anomaly, whereas two patients were hospitalized in an intensive care unit for decompensated heart failure due to congenital heart disease. Finally, one patient presented with respiratory distress in the newborn with a poly-malformative syndrome at the time of diagnosis. The karyotype performed confirmed the diagnosis of trisomy 18 free and homogeneous in all five patients, and genetic counseling was performed. Genetic counselling is a specialized preventive medicine consultation, which allows the risk of recurrence to be calculated for any chromosomal anomaly, including Edwards syndrome. Thus, for a couple with a child with free and homogeneous trisomy 18, the probability of recurrence in the next pregnancy is 1%. In cases where trisomy 18 is partial, and therefore secondary to a structural anomaly, it is necessary to perform a karyotype in the parents to eliminate carriers with a balanced translocation, because the probability of recurrence is greater. The incidence of trisomy18 also increases with advanced maternal age. Furthermore, the complexity and severity of the clinical picture and the high rate of neonatal and infant mortality emphasize the importance of prenatal diagnosis of this disease.
Keywords
trisomy18, facial dysmorphia, prenatal diagnosis.
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EP948

Klinefelter syndrome diagnosed late in a person with motor and cerebral infirmity
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Introduction
Klinefelter syndrome is a genetic condition that results when a boy is born with an extra copy of the X chromosome. Klinefelter syndrome is a genetic condition affecting males, and it often isn't diagnosed until adulthood. It is manifested by gynecomastia, small testicles, erectile dysfunction, infirtility …
Observation
70-year-old male patient with motor and cerebral infirmity, several fractures following minimal trauma. Hospitalized for imbalance of type 1 diabetes and the clinical examination found bilateral gynecomastia, microtesticles and the patient was beardless. Bone densitometry shows severe osteoporosis. Testosterone was low at 1.1 nmol/l, FSH high at 28.3 IU/l, LH also high at 11.1 IU/l. Karyotype analysis revealed a 47 XXY chromosome formula.
Conclusion
Klinfelter syndrome diagnosed late, masked by mental retardation, Consider examining patients and requesting a hormonal assessment in the presence of trabecular osteoporosis.
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EP949

Primo-secondary amenorrhea: When autoimmune polyendocrine syndrome divert the course of a Rathke's cleft cyst
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Introduction
Secondary or primo-secondary amenorrhea suggests central damage of the hypothalamic-pituitary axis or peripheral damage of the reproductive system. It must be carefully investigated with an essential hormonal workup to determine the etiology and initiate the appropriate treatment.
Observation
We report the case of a 21-year-old patient, admitted for exploration of a primo-secondary amenorrhea associated with a pituitary tumor syndrome made of retro-orbital headaches, without vomiting nor visual acuity decrease, with sometimes hot flashes. Clinically, the patient had a good development of secondary sexual characteristics. She was in clinical euthyroidism without dysmorphic syndrome. Biologically: 17 B Estradiol was less than 12 pg/ml with elevated gonadotropins, collapsed AMH and normal karyotype. Anti-TPO antibodies were positive with normal TSHus. Radiologically: Hypothalamic-pituitary MRI revealed of a Rathke's cleft cyst of 6 mm and uterus was hypoplasic on Pelvic ultrasounds. Finally, Eye examination and Goldman's visual field were normal.
Discussion-Conclusion
This observation reflects the complexity of the etiological diagnosis of primo-secondary amenorrhea while two disorders at different levels of the hypothalamic-pituitary-ovarian axis are associated: Rathke's cleft cyst and primary autoimmune ovarian insufficiency as part of a type 2 autoimmune polyendocrine syndrome. Thus, although the diagnosis may be obvious, further investigation should be required to support the diagnosis and to avoid misinterpretation of a true underlying etiology.
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EP950

Curschmann Steinert disease and related endocrine disorders
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Introduction
Steinert's myotonic dystrophy (SMD) is a neuromuscular disorder with a multisystem distribution. It is a genetic disease with autosomal dominant transmission. It may be associated with various endocrine disorders.

Observation
We report the case of a 47-year-old patient followed for DM since the age of 18, diabetic under insulin therapy for 20 years, hypertensive for 1 year under losartan 50 mg/d who was referred to us for evaluation of the endocrine impact of his disease. On examination, the patient reported significant asthenia, polyuropolydipsic disorder with 5 nocturnal awakenings, erectile dysfunction, decreased libido and weight gain. Examination: conscious patient, with significant psychomotor slowing down, bilateral congenital ptosis, overweight (BMI = 26.2 kg/m2), normocardial at 91bpm, his blood pressure was 148/72 mmHg, areas of lipodystrophy on the left arm, his thyroid was not palpable. External genitalia examination was normal, her osteotendinous reflexes were weak. On biology, the HbA1c was 12.60%, the thyroid balance: TSH: 1.32 mIU /l T4 21.2pmol/l, the testosteronemia was 4.96 mg/l with gonadotropins: FSH at 4.5 ui /l and LH at 6.7ui /l and a normal prolactinemia, the lipid balance objectified a total hypercholesterolemia at 2.98g/l. The management was based on the reinforcement of the hygienic-dietary rules, the intensification of the insulin therapy and the setting on atorvastatin. The evolution was favorable.
Discussion
Steinert's myotonic dystrophy is the most common muscular dystrophy in adults [1]. It is an autosomal dominant inherited neuromuscular disorder characterized by myotonia and progressive muscle atrophy. It is multisystemic and highly variable in clinical expression [2]. The endocrine abnormalities most commonly associated with DSM are dysthyroidism, diabetes, peripheral gonadal insufficiency, increased risk of hyperlipidemia, nonalcoholic fatty liver disease, erectile dysfunction, benign and malignant thyroid nodules, bone fractures, miscarriage, premature delivery, and labor failure during delivery. Circulating levels of parathyroid hormone and corticotropic hormone may be elevated, but the mechanisms of these associations are unclear [3-4]. DM is responsible in our patient for poorly controlled diabetes and total hypercholesterolemia. The thyroid workup ruled out hypothyroidism despite the suggestive clinical signs, hypogonadism was also ruled out.
Conclusion
DM does not only concern the neurologist, but requires a multidisciplinary management in which the endocrinologist finds his place both in the screening and in the management. A systematic search for endocrinopathies could help prevent certain complications.

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Thyroid

EP951

Application of a novel multimodal-based deep learning model for prediction of recurrence in patients with papillary thyroid carcinoma

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Background
Thyroid cancer is the most common endocrine malignancy, and papillary thyroid carcinoma (PTC) is the most frequent type of thyroid malignancy. Although the mortality rate is low, some patients experience cancer recurrence during follow-up periods. Early detection of recurrence helps improve the outcomes of patients and reduce the socioeconomic burden. In this study, we investigated the accuracy of a novel multi-modal prediction model by simultaneously analyzing numeric and time-series data to predict recurrence in patients with PTC after thyroidectomy.
Methods
We analyzed patients with thyroid carcinoma who underwent thyroidectomy at Chungbuk National University Hospital between January 2006 and December 2021. To detect PTC recurrence, we acquired clinical data, including demographic information, ultrasonography (US) reports, pathology reports, whole-body iodine scan, and thyroid function test results. We propose a novel multimodal-based deep learning model for predicting PTC recurrence. The proposed model uses numerical data, including clinical information at the surgery, and time-series data, including TFT results after the surgery. For the model training with unbalanced data, we employed weighted binary cross-entropy with weights of 0.8 for the positive (recurrence) group and 0.2 for the negative group.
Results
Our dataset consists of 1,613 patients, including patients who 1,550 non-recurrence PTC and 63 recurrence PTC, who underwent thyroidectomy. Patients with recurrence had larger tumor size, more multiplicity, and a higher frequent male ratio than those without recurrence. We performed 4-fold cross-validation on the dataset to evaluate the model performance. The proposed model achieved an average AUROC of 0.9622, F1-score of 0.4603, sensitivity of 0.9042, specificity of 0.9077. When applying our proposed model, experimental results show that it can predict recurrence at least one year before recurrence.
Conclusions
Our study results demonstrated that the multi-modal prediction model for predicting PTC recurrence after thyroidectomy showed good performance. In clinical practice, it might help in the early detection of recurrence during follow-up in patients with PTC after thyroidectomy.

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EP952

Alemtuzumab-Induced Severe Ophthalmopathy in Relapsing-Remitting Multiple Sclerosis: Experience at A Single Center

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Objectives
To identify risk factors for the development of Graves' Orbitopathy (GO) in patients with Relapsing Remitting Multiple Sclerosis (RRMS) treated with Alemtuzumab, as well as to analyze the clinical behavior of this entity based on a case series.
Methods
Retrospective observational study with real-life data. Patients with RRMS who received at least one cycle of Alemtuzumab in the period 2014-2022 in aMS reference unit in Spain were included. During post-treatment follow-up, the development of Graves' disease (GD) and GO was documented in the included cases, being assigned to one of three possible subgroups: a) No GD or GO, b) GD without GO, c) GD and GO.
Results
134 patients were included. Mean follow-up was 5.98 years (SD:3.23) since initiation of Alemtuzumab. 90/134 cases (67.1%) had neither GD nor GO, 38/134 (28.4%) had GD without GO and 6/134 (4.5%) had GD and GO. The incidence of GO in patients with GD was 13.64% ($n=6/44$). The annual of pre-Alemtuzumab outbreak rate was higher in the group that developed GO (2.4 vs 1.39 GD-noGO and 1.38 noGD-noGO, $P=0.03$), as was the presence of first-degree family history of autoimmune hypothyroidism (33.3% vs 13.2% GD-noGO and 5.2% noGD-noGO, $P=0.017$). Cases that developed GO presented with respect to the GD-noGO group higher levels of f-T4 (4 vs 2.3 ng/dl, $P=0.009$), f-T3 (13 vs 6.2 pg/ml, $P=0.033$) and TRab (34.77 vs 16.27 IU/l, $P=0.016$), in addition to clinical symptomatology (83.3% ($n=5/6$) vs 38.9% ($n=14/38$), $P=0.04$) and goiter (83.3% ($n=5/6$) vs 23.5% ($n=8/38$), $P=0.01$). The need for total thyroidectomy was higher in the group that developed GO (66.7% ($n=4/6$) vs 18.4% ($n=7/38$), $P=0.027$). Of the 6 diagnosed cases of GO, $n=3$ were moderate/severe and active forms (mean CAS: 4.3 points). Treatment with Tocilizumab (anti-IL6) was indicated in all of them due to refractoriness to corticosteroid treatment ($n=1/3$) or contraindication to it ($n=2/3$). In all three cases, inactivation of the disease (CAS <3) was documented after Tocilizumab, with improvement of proptosis and palpebral retraction. No retraction surgery was indicated in any case.
Conclusions
The presence of first-degree relatives with hypothyroidism, a high annual baseline outbreak rate or the development of GD with high levels of f-T4, f-T3 and TRAb can be considered risk factors for the development of GO in patients treated with Alemtuzumab. Treatment with Tocilizumab may be a useful option in the treatment of cases with elevated activity index.

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EP953

COVID-19 – a trigger of autoimmune thyropathy disorders?

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Introduction
Research into autoimmune disorders associated with COVID-19 in the middle of an ongoing COVID-19 pandemic is an important and urgent challenge. We focus on the potential relationship between coronavirus infection and other autoimmune diseases, and the positive therapeutic effect of the treatment of severe forms of COVID-19 with drugs traditionally used in the treatment of rheumatological diseases. The results of this study are a starting point for understanding the mechanisms of related to potential breakdown of immunological tolerance and the development of thyroid autoimmune diseases during COVID-19.
Materials and Methods
This prospective single-center, case-control study included 41 patients hospitalized at the National Endocrinology Research Centre with a clinical and laboratory analysis diagnosis of COVID-19 and bilateral polysegmental viral pneumonia, as well as 78 healthy individuals who have never had a coronavirus infection. Both groups were comparable in terms of gender and age. To assess the functional status of the thyroid gland all patients underwent observation of the thyroid-stimulating hormone (TSH), T3free, T4free, antibodies to thyroid peroxidase, antibodies to the TSH receptor. Their thyroid profile was assessed in both the acute period of the disease as well as 6 months after recovery. The markers of the inflammatory process were assessed: 27 signal molecules of cytokines and chemokines. In patients from the first group, the study of the following cytokine levels was carried out in both the acute period of the disease as well as 6 months after recovery: IL-1b, IL-1ra, IL-2, IL-4-10, IL-12, IL-13, IL-15, IL-17, Eotaxin, FGF, GM-CSF, G-CSF, IFN-g, IP-10, MCP- 1, MIP-1a and -1b, PDGF-bb, RANTES, TNF-a, VEGF.
Results
Manifest hypothyroidism was detected in 2.4% of patients, and at subclinical levels in 7.3% of patients 6 months after the onset of coronavirus infection, in addition to an increase in antibodies to thyroid peroxidase 6 months after recovery from coronavirus infection was detected ($P = 0.023$). In the group of patients with increased antibodies to thyroid peroxidase after undergoing COVID-19, statistically significantly high levels of IL-4 ($P = 0.033$), IFN-g ($P = 0.007$), and Eotaxin ($P = 0.008$) were obtained. An increase in antibodies to the TSH receptor was revealed in the group of patients with severe COVID-19 who did not receive pathogenetic therapy with tocilizumab in the acute period of the disease ($P = 0.046$).
Conclusion
Our research shows that the COVID-19 may be a trigger of autoimmune thyropathy disorders.

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EP954

The reduction of peripheral blood Treg differentiated fractions and the CD25 expression in Patients with Graves' disease after Radioactive Iodine Therapy

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Background
Foxp3(+) regulatory T cells (Treg) play a leading role in developing immune tolerance through active suppression in Graves' disease (GD). The influence of radioactive iodine therapy (RAI) on the differentiated fractions of Treg of GD patients is still poorly understood.
Aim
To estimate the differentiated fractions of blood Tregs and the CD25 expression in patients with GD after RAI.
Materials and Methods
In total, 36 women with recurrent GD (age mean [range] = 46.34 ± 14.32 years [27–59] and 42 age-and sex-matched healthy control subjects were recruited into the study. All patients treated with thiamazole for at 5 months (2 – 9) and withdrawal 14 days before RAI. All patients had a fixed 400-700 MBq radioactive iodine (^{131}I) dose orally. For the immunophenotyping of Treg differentiating fractions, each whole blood sample (100 μL) was stained using FITC-labeled mouse anti-human CD62l, PE-labeled mouse anti-human CD127, ECD-labeled mouse anti-humanCD45R0, PC5.5-labelled mouse anti-human CD25, PC7-labelled mouse anti-human CD4 (clone T4, cat. 6607101, Beckman Coulter, Indianapolis, IN, USA), A-A700-labelled mouse anti-human CD3 and A-A750-labelled mouse anti-human CD45. The CD25 expression assessed by MFI.
Results
Lower absolute counts of Treg ($CD3^+CD4^+CD127^{Low}CD25^{High}$) were found in GD patients before RAI in comparison with healthy controls ($P < 0.001$). In GD patients up to six month after RAI the absolute and percentage Tregs content was lower relative to initial levels ($P < 0.001$). In GD patients before and 1, 3 and 6 month after RAI a significant decrease in the percentages of "naïve" ($CD45R0^-CD62L^+$) and terminally differentiated ($CD45R0^-CD62L^-$) Tregs was established relative to the control, and on 3 and 6 months after RAI a significant decrease of this Treg differentiated fractions was observed relative to the values detected in patients before and 1 month after RAI ($P < 0.001$). Against the background of compensated hypothyroidism in GD patients on 3 and 6 months after RAI we observed a significant decrease than in healthy individuals in expression of MFI CD25 on "naïve" and terminally differentiated Tregs ($P < 0.001$), and central memory Tregs ($CD45R0^+ CD62L^+$) ($P < 0.001$).
Conclusion
There is expanding knowledge on new Treg imbalance that is crucial for the development of GD. The role and importance of "naïve" and terminally differentiated Treg in the pathogenesis of GD allows not only a better understanding of the mechanisms of development and reccurence of these diseases, but also helps to define immunotherapy targets that can be restored by increasing the number and function of Tregs.

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EP955

Oxidative stress and the level of NAD(P)-dependent dehydrogenases of blood neutrophils in patients with compensated and relapse Graves' hyperthyroidism ongoing thiamazole treatment

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Background
Oxidative stress is involved in the pathogenesis of Graves hyperthyroidism (GH) and a disbalance of the cell redox state is associated with thyroid hyperfunction and the reccurence of the disease.
Aim
To study the level of reactive oxygen species (ROS) and NAD(P)-dependent dehydrogenases of peripheral blood neutrophils in patients with compensated and relapse GH ongoing thiamazole.
Materials and Methods
The study included 96 women with onset of Graves' disease, aged 20 to 65 years, ongoing thiamazole. At the follow-up examination three months after the start of thiamazole all patients divided into two groups, respectively, compensated and relapse hyperthyroidism. The level of ROS was studied using a 36-channel chemiluminescence analyzer "BLM-3607" and characterized by: Tmax – the rate of chemiluminescent reaction, Imax - the maximum level ROS synthesis and the area under the chemiluminescence curve (S - total synthesis of ROS for 90 minutes). The activity of NAD(P)-dependent dehydrogenases in neutrophils was determined using the bioluminescent method.
Results
In relapse GH patients, the indicator S of spontaneous and zymosan-induced lucigenin-dependent chemiluminescence increases significantly, both relative to the control and to the values of GH compensated patients ($P < 0{,}001$). Luminol-dependent chemiluminescence in GH relapsed patients demonstrated more than tenfold increase of S relative to the control, but no statistically significant differences were found in GH compensated patients. In GH patients both groups the activity of the studied NAD-dependent oxidoreductases (NAD-GDH and MDH), auxiliary dehydrogenase reactions (NADP-GDH and NADP-ICDG) and NADH-dependent reactions (NADH-LDH and NADH-MDG) is increased ($P < 0{,}001$). A high level of NADH-dependent glutamate dehydrogenase was observed in GH relapse patients, both relative to the control and GH compensated patients ($P < 0{,}001$). In GH compensated patients compared to control the low activity of Lactate dehydrogenase was revealed ($P < 0{,}001$). In GH relapse patients the

levels of G6PDH and NADP-GDH activity are correlated with S spontaneous lucigenin-dependent chemiluminescence ($r = 0.74$, $P < 0.001$, in both cases) and Imax spontaneous luminol-dependent chemiluminescence ($r = 0.69$, $P = 0.003$ and $r = 0.65$, $P = 0.005$, respectively).
Conclusion
In GH compensated patients the level of oxidative stress mainly affects the primary ROS production, which is associated with hyperthyroidism compensation and the immunosuppressive effect of thiamazole. In GH relapse patients, there are more changes in the production of secondary ROS, indicating the activation of cellular response immunological mechanisms, that determined by the features of intracellular metabolism and may play an important role in the recurrence of the disease.

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EP956

Conversion from longstanding hypothyroid Hashimoto's thyroiditis to Graves' disease. Clinical characteristics from a large patient cohort

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The transition of hypothyroidism from Hashimoto's thyroiditis into hyperthyroidism (Graves' disease) is uncommon, and the underlying causes are still unknown. We studied clinical characteristics in patients with the conversion of preexisting Hashimoto's thyroiditis to Graves' disease compared to patients with Hashimoto's thyroiditis or Graves' disease alone.
Patients and Methods
Retrospective comparative case series of 42 patients (mean age 53 years, 95%-CI [47.9;58]) with preexisting hypothyroidism due to Hashimoto's thyroiditis who developed hyperthyroidism (Graves' disease with positive TSH receptor antibodies). Data were compared with 30 patients with Hashimoto's thyroiditis (mean age 48.5 years, 95%-CI [44;53]) and 38 patients with Graves' disease (mean age 48.5 years 95%-CI [44;53.9]). In all three groups, female patients were predominant (Female to male ratio case group 38:4, Hashimoto group 26:4 and Graves' disease 36:2). Social data (age, sex, origin, marital status, number of children, residential environment, occupational status, stressful life events, smoking, and alcohol), clinical data (body mass index, concomitant diseases, concomitant medication, therapy for thyroid dysfunction) and biological data (TSH, freeT3, free T4 and thyroid antibodies) were analyzed.
Results
Hypothyroid patients were treated for a mean time of 12.2 years before they developed hyperthyroidism. The mean dose of levothyroxine to maintain euthyroidism was 92 micrograms per day. Before manifestation of hyperthyroidism, patients who converted to Graves' disease showed significantly higher TSH values (Wilcox-test $P=0.003$) and significantly lower T4 values (Wilcox-test $P=0.02$) than patients with Hashimoto's thyroiditis alone. Compared to patients with Hashimoto's and Graves' disease, conversion patients were significantly more likely to take concomitant medications. No significant difference was found in the social factors of patients with conversion compared with Hashimoto's and Graves' disease controls. Alcohol consumption and smoking status were comparable. No differences were seen in TSH, T3 and T4 levels in hyperthyroidism between conversion patients and patients with Graves' disease and in the distribution of thyroid-specific antibodies between case and control patients.
Conclusion
Smaller case series have been published regarding patients with conversion from Hashimoto's thyroiditis to Graves' disease. So far, our study is the largest case series and the only one with a comparison of patients with Hashimoto's thyroiditis or Graves' disease alone. There was a significant difference in the TSH and T4 levels between conversion patients before manifestation of Graves' disease and Hashimoto's patients. No difference could be seen in the other clinical parameters. In the future, genetic and immunological studies may identify factors separating these disease entities better.

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EP957

Rising preoperative TPO titers decrease the risk for differentiated thyroid cancer in a linear fashion: a retrospective analysis of 1620 consecutive thyroid surgeries

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Introduction
Chronic lymphocytic thyroiditis is an important risk factor for differentiated thyroid cancer (DTC) in surgical series, but the role of thyroid peroxidase antibodies (TPO) seems less clear in that regard. We designed the present study to evaluate that effect in our large patient population.
Methods
We recruited subjects operated with total thyroidectomy in 4 sites (USA: 1, Greece: 3) during a period of 14 consecutive years. We gathered data on TPO antibodies titers measured with commercially available radioimmunoassays, and reviewed data on surgical pathology. TPO $\geq$ 34IU/ml was deemed high (TPO+). Odds ratios (OR) for DTC were calculated with Fischer's exact test. $P < 0.05$ was deemed significant.
Results
We reviewed data on 8,425 thyroid surgeries, and TPO titers were available for 1,620 subjects: DTC $n=702$ (43.3%), benign pathology (BEN) $n=918$ (56.7%), TPO+ $n=524$ (32.3%) and TPO- (<34IU/ml) $n=1096$ (67.7%). DTC was found with a lower frequency in TPO+ (183/524, 34.9%) compared to TPO- (519/1096, 47.4%) subjects, OR 0.60 (0.48-0.74, $P < 0.0001$). Subjects with the lowest TPO titers had the highest rate of DTC: TPO< 10IU/ml $n=338/635$ (49.3%), TPO 34-100IU/ml $n=69/162$ (42.6%), TPO 100-500IU/ml $n=70/168$ (41.7%), TPO 500-1000IU/ml $n=16/50$ (32.0%), TPO >1000IU/ml $n=28/144$ (19.4%), $P < 0.0001$.
Conclusions
High TPO Antibodies appear protective against DTC in our large multicentre cohort of patients operated with a total thyroidectomy. Rising preoperative TPO titers confer linearly increasing protection against DTC in the surgical specimen. More research is needed to fully understand the role of thyroid autoimmunity in the genesis of DTC.

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EP958

Accuracy of the European Thyroid Imaging Reporting and Data System (EU-TIRADS)

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Introduction
There are several classifications based on thyroid ultrasound for selecting suspected malignant thyroid nodules. In 2017 the European Thyroid Association developed a new and simple European Thyroid Imaging and Reporting Data System (EU-TIRADS), which classifies the risk of malignancy of thyroid nodules in adults to the following categories: benign, low-, intermediate-, and high-risk.
Objective
To evaluate the accuracy of the EU-TIRADS for detecting malignant thyroid nodules.
Methods
A retrospective study of 213 patients (335 nodules) who underwent thyroid surgery at our ENT department, from 2013 to 2021. Histological results were correlated to the ultrasound findings.
Results
Our study included 193 women and 20 men. The mean age was 46,8 years. The percentage of each EU-TIRADS class was: EU-TIRADS 2 = 12,8 %, EU-TIRADS 3 = 43,9 %, EU-TIRADS 4 = 7,2 % and EU-TIRADS 5 = 36,2%. Thyroid cancer was noted in 14,6% and 85,4% of the cases had benign nodules. The risk of malignancy was: EU-TIRADS 2 = 4,6 %, EU-TIRADS 3 = 6,1 %, EU-TIRADS 4 = 8,3 % and EU- TIRADS 5 = 80,09 %. Correlation of histological results with preoperative ultrasound findings showed a sensitivity of 77,55%, a specificity of 62,95% with positive and negative predictive values of 26,21% and 94,21% respectively.
Conclusion
To conclude, EU-TIRADS is a simple tool in assessing the malignancy of thyroid nodules, which demonstrates a good clinical correlation with histological results. Because of its good sensitivity it can be used in selecting nodules with a high risk of cancer.

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EP959

Anasarca state with exceptional localization revealing a deep hypothyroidism

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Introduction
Hypothyroidism-related anasarca is due to the capillary permeability disorders associated with hypothyroidism. It is a rare mode of revelation especially when associated with ascites, which is an exceptional localization. We report the case of a deep hypothyroidism revealed by an ascites of great abundance.
Observation
Our patient is 73 years old with a history of 2 daughters followed for Hashimoto's thyroiditis. He consults for abdominal distension associated with hoarseness, hypoacusis and constipation evolving for 3 months.. Clinical examination revealed cutaneous-mucosal infiltration, dry scaly skin and abundant ascites with positive flot sign without collateral venous circulation. The diagnosis of Hashimoto's thyroiditis was retained in view of an elevated TSHus at 150 Uui/ml; a low LT4 at 2.48 pmol/l; very positive anti thyroperoxidase antibodies $>$ 1000 UI/ml and an appearance of thyroiditis on cervical ultrasound. The ascites fluid study showed a sterile exudative fluid without malignant cells with a negative GeneXpert tuberculosis. The transthoracic echocardiography showed a pericardial effusion slide and the thoraco-abdomino-pelvic CT scan did not reveal any tumor focus apart from a large ascites and a small bilateral pleurisy. Hormone replacement therapy was started progressively at a dose of 75 µg/dl of L-thyroxine allowing the progressive disappearance of ascites and signs of hypo metabolism.
Conclusion
Exudative ascites remains a rare location of myxedematous hypothyroidism. Our case underlines the importance of F-T4 and TSH assay in the etiological assessment of ascites of undetermined cause and particularly in elderly subjects. This allows to avoid useless explorations which can, in rare cases, lead to the death of the patient in a myxedematous coma.

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EP960

Rare case of Graves' disease resistant to methimazole: a case report

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Introduction
The treatment of Graves' disease is represented principally by anti-thyroid drugs, radioiodine ablation or thyroidectomy. Methimazole is the most used drug for the initial treatment. It is rare to encounter patients with resistant hyperthyroidism despite high doses of MMI.
Case presentation
A 41-year-old woman was referred to our unit for resistant thyrotoxicosis. She had a confirmed Graves' disease with positive serum Trab. Whilst her MMI dose had been increased to 60 mg/day, in adjunction with prednisone therapy (70 mg/day), her serum free thyroxin concentration was too high to be measured ($>$ 100 pmol/l). No adverse effects were noted. The patient did not show any symptoms or signs of gastrointestinal or liver disease, and had good drug compliance. Additional therapy with inorganic iodine (Lugol solution 10 drops 3 times /day) was initiated and she underwent a therapeutic plasma exchange. After 10 days, the patient's serum free thyroxin concentration normalized, and total thyroidectomy was then performed.
Discussion
It is rarely reported that cases of Graves' disease show no response to a very high dose of MMI and corticosteroid therapy. By preventing the iodination of tyrosine residues in thyroglobulin by thyroid peroxidase, MMI inhibits thyroid hormone synthesis. A previous clinical study showed that a high dose of MMI (120 mg/day) reduces thyroid hormone concentration more rapidly than standard doses of MMI in patients with hyperthyroidism. However, such a high dose of MMI may increase the risks of severe adverse effects. Therefore, we decide to maintain the MMI dose of 60 mg/day for our patient. Although previous cases of Graves' disease with resistance to antithyoid drugs has been reported, the underlying mechanisms remain unclear. Inorganic iodine inhibits the release of thyroid hormone from the thyroid gland, and corticosteroids work by suppressing the conversion of T4 to T3 in peripheral tissues. The Japan Thyroid Association and the Japan Endocrine Society recommended strategy is combination of MMI with corticosteroid and inorganic iodine in preparation for a thyroidectomy.
Conclusion
We reported a rare case of Graves' disease that was resistant to MMI. Combination therapy of MMI with corticosteroid, inorganic iodine and therapeutic plasma exchanges may represent a therapeutic option for the preoperative preparation.
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EP961

Alemtuzumab-Induced Autoimmune Thyroid Dysfunction. A review of two cases

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Introduction
Alemtuzumab is an humanized monoclonal antibody used for treatment of Relapsing remitting Multiple Sclerosis (RRMS). One of its main adverse effects is thyroid dysfunction, being a fluctuating hypothyroidism the most frequent presentation. Sometimes this thyroid disturbance is so significant that it might lead to alemtuzumab withdrawal. We present two Clinical cases of hyperthyroidism secondary to alemtuzumab with different clinical courses.
Case 1
53-year-old woman with RRMS **under** treatment with alemtuzumab (1 cycle received in 2019). She was referred by the Neurology Department due to thyroid disturbance (TSH 0.2 mcU/ml) prior to starting a new cycle. Laboratory tests showed previous normal TSH values but with positive autoimmunity (TgAb and TPOAb). She was asymptomatic so clinical monitoring was decided. The patient experienced progressive clinical and analytical development of severe hyperthyroidism in the follow-up, so antithyroid drugs (ATD) were **prescribed**. The study was completed with an ultrasonography and radionuclide scintigraphy, which showed diffuse hypercaptant goiter; and antibodies (TRAb positive). ATD was prescribed, and she was progressively improving. After that, the patient developed several relapses after lowering the dose. For this reason, we considered treatment with radioiodine, which was effective.
Case report 2:
43-year-old woman with RRMS since 2019, **under** treatment with alemtuzumab and autoimmune thyroid disease since 2013, with normal function. Two months after the start of treatment with alemtuzumab, she consulted about severe hyperthyroidism. The study consisted of an ultrasonography and radionuclide scintigraphy, which showed diffuse hypercaptant goiter; and antibodies (TRAb positive). The patient presented spontaneous evolution to severe hypothyroidism two months later. We started substitution treatment, and during follow-up, the patient presented two relapses of hyperthyroidism, which was resolved after discontinuation of replacement therapy. Currently, the patient is followed and checked every six months showing thyroid stability.
Conclusions
Alemtuzumab, an effective disease-modifying drug therapy for relapsing-remitting multiple sclerosis, frequently causes autoimmune thyroid dysfunction in a significant proportion of patients. Graves' disease and Hashimoto's thyroiditis can have similar clinical presentations. In alemtuzumab-induced autoimmune thyroid dysfunction, additional challenges are posed by spontaneous, bidirectional switching between hyperthyroidism and hypothyroidism. Guidelines recommend monitoring thyroid function pre-treatment and every three months for four years post-treatment.

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EP962

A systematic review and meta-analysis on the associations of maternal iodine status and supplementation with thyroid function during postpartum

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Background
Iodine deficiency and excess are well-recognized risk factors for thyroid dysfunction. This systematic reveiw and meta-analysis was designed, for the first time, to explore whether maternal iodine status or supplementation is associated with postpartum thyroid function.
Methods
Electronic databases, including the MEDLINE/PubMed, Web of Science, Embase, and Scopus were searched between January 1923 and December 2021 to identify relevant studies. We assessed the quality of studies using the Newcastle-Ottawa scale. The pooled mean thyroid stimulating hormone (TSH), free thyroxin (fT4), and thyroxin (T4) concentrations and 95% confidence intervals (CIs) were estimated based on maternal iodine status. Iodine status was defined based on median values <100 and ≥ 100 µg/l for urinary iodine concentration (UIC) or breast milk iodine concentration (BMIC) during postpartum. We used a fixed/random effect model based on the absence/presence of heterogeneity. A narrative synthesis of the data was performed for iodine supplementation.
Results
Of the 2175 studies were identified, 18 were eligible for inclusion in the meta-analysis. Thyroid hormones in women who had UIC $\geq$ 100 µg/l were higher than those of women with UIC <100 µg/l during the postpartum period. The pooled values [95% CI] for TSH, fT4, and T4 concentrations in iodine-sufficient women were 1.31 [1.09, 1.53] mIU/l, 14.26 [13.86, 14.66] pmol/l, and 91.97 [88.61, 95.33] nmol/l, respectively; whereas the corresponding values in iodine-deficient women were 1.00 [0.84, 1.16] mIU/l, 12.26 [10.49, 14.03] pmol/l, and 79.80 [59.53, 100.07] nmol/l, respectively. However, none of these differences was significant. The concentration of thyroid hormones in women with BMIC <100 µg/l and ≥ 100 µg/l were within the normal range. Iodine supplementation was administered from 1 week to 9 months postpartum as supplements doses from 75 to 300 µg oral iodine daily ($n=3$) or a single 400 mg dose of iodized oil ($n=1$). In none of these, significant differences in thyroid parameters of postpartum women between the iodine-supplemented and control groups were observed.
Conclusion
Findings of the present systematic review and meta-analysis showed no effects of iodine status or supplementation on thyroid hormones in postpartum women. Further investigations are still needed to explore the effects of different degrees of iodine deficiency as well as iodine excess on different maternal thyroid parameters during postpartum and effects on thyroid function in breastfed offspring.

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EP963

Frequency of Coeliac Disease in Children with Chronic Autoimmune Thyroiditis

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Introduction
Chronic autoimmune thyroid disease (ATD) or Hashimoto thyroiditis (HT) is one of the main thyroid diseases in pediatric age. HT characterized by the production of anti-thyroid antibodies, by an infiltration of autoreactive B and T lymphocytes into the thyroid parenchyma and by alterations in thyroid function. Coeliac disease (CD) is a systemic autoimmune disease caused by gluten ingestion in genetically predisposed subjects. At presents with a pathognomonic enteropathy, a variety of clinical manifestations, positivity for specific antibodies, positivity for typical haplotypes HLA DQ2/DQ8. The close relationship between celiac disease and glandular autoimmunity can be largely explained by sharing of a common genetic background. Haplotypes HLA B8 and DR3 occur with increased frequency in adults and children with CD, as well as in ATD. Modern international recommendations recommend screening for CD in children with already diagnosed ATD.
The aim
of this study was to investigate the incidence of celiac disease in children with ATD.
Methods
65 children with ATD aged 7-17 years (57 girls, 8 boys) were examined. We studied the level of TSH, free T4, antibodies to thyroperoxidase (Anti-TPO), antibodies to thyroglobulin (Anti-TG) gliadin immunoglobulin G (Anti-IgG Gl), anti-tissue transglutaminase (Anti-IgG TGT), ultrasound of the thyroid gland (US ThG). Diagnosis of autoimmune thyroiditis was made if Anti-TPO >35 IU/ml or Anti-TG >20 IU/ml. Diagnosis of CD was made according recommendation from the European Society for the Study of Coeliac Disease (ESsCD) (2019).
Results
Among the children with ATD 32.3% ($n=21$) were diagnosed with hypothyroidism, the patients received levothyroxine replacement therapy and were in a state of medical euthyroidism at the time of inclusion in the study. CD was detected in 10.8% ($n=7$, all girls) of the patients. The mean age (12.5 $\pm$ 1.6 yrs) at the diagnosis of HT was significantly lower in patients with higher levels Anti-TPO (432.2 $\pm$ 23.8 IU/ml) and Anti-TG (86.6 $\pm$ 12.5 IU/ml). After prescribing a gluten-free diet for 6 months to children with a positive level of Anti-IgG TGT, patients showed a statistically significant decrease in the level of Anti-TPO and in 3 patients (280.4 $\pm$ 18.2 IU/ml) and decrease the dose of levothyroxine by an average of 30%.
Conclusion
Frequency of CD in children with ATD was 10.8%. Gluten-free diet for 6 months has some effect on improving and maintaining euthyroid status of CD patients and decreased anti-thyroid antibodies.

Keywords
Autoimmune thyroid disease; Coeliac disease; Gluten-Free Diet.
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EP964

Factors associated with elevated liver enzymes in patients with uncontrolled hyperthyroidism

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Liver dysfunction is common in patients with hyperthyroidism. The underlying mechanisms remain unclear. Predictors of liver dysfunction and recovery are controversial. The aim of this study was to assess the prevalence of elevated liver enzymes in patients with uncontrolled hyperthyroidism and to identify its predictive factors.
Methods
This is a retrospective study conducted in 131 patients with hyperthyroidism admitted in the endocrinology department of La Rabta Hospital (Tunisia) between January 2009 and December 2018. Patients with subclinical hyperthyroidism and those with controlled thyroid function under treatment were not included. Liver enzymes: Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured in all the patients at admission. Clinical and biological data were reviewed to identify factors associated with elevated liver enzymes (AST and/or ALT) using univariate and multivariate analysis.
Results
The mean patient age was 44.1 $\pm$ 16.9 years. They were 52 men (39.7%) and 79 women (60.3%). Hyperthyroidism was related to Graves' disease in 74.8% of cases. The mean AST level was 25.6 $\pm$ 18.4 UI/l (normal range: 5-34). It was elevated in 16.0% of patients. The mean ALT level was 28.8 $\pm$ 22.5 UI/l (normal range: 6-55). It was elevated in 8.4% of patients. Elevated liver enzymes (AST and/or ALT) have been observed in 18.3% of cases. FT4 levels were significantly higher in patients with elevated liver enzymes (6.0 $\pm$ 4.2 vs 4.3 $\pm$ 2.1 ng/dl, $P=0.006$). FT4 higher than 4 times normal range was associated with elevated liver enzymes (41.7% vs 19.6%, $P=0.02$, OR [95%CI] = 2.9 [1.2-7.4]). Age, gender, smoking status, BMI, etiology of hyperthyroidism, and anti-TSH receptor antibody levels were not associated with elevated liver enzymes. After adjustment for age and gender, FT4 level higher than 4 times the normal range remains an independent parameter associated with elevated liver enzymes ($P=0,05$; ORa [95%CI] = 2.5 [1.0-6.7]).
Conclusion
Elevated liver enzymes are common in hyperthyroidism. The biological severity of hyperthyroidism seems to be the main predictive factor of this liver dysfunction.

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EP965

The role of PTEN methylation level changes in papillary thyroid carcinoma diagnosis and prognosis

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Introduction
Papillary thyroid cancer (PTC) is the most common type of thyroid cancer (85%–90%). Today Fine needle aspiration biopsy (FNAB) is the diagnostic tool for the evaluation of thyroid nodules because of its accuracy and cost-effectiveness, but FNAB also has limitations, as it is quite challenging to take a biopsy from a small thyroid nodule moreover FNAB diagnosis is doubtful in up to 20% of cases. Therefore, non-invasive biomarkers of PTC are needed.
Aim of the study
To evaluate methylation level changes of the PTEN gene in FFPE tissue samples and peripheral blood plasma samples of PTC patients before and after surgery.
Methods
The study included 50 FFPE tissue samples from 25 patients and 68 patients plasma samples with a histologically confirmed diagnosis of PTC. Peripheral blood samples were collected before surgery and 4-6 weeks after surgery. Methylation level changes of the PTEN gene were analysed in plasma and FFPE tissue samples by quantitative methylation-sensitive polymerase chain reaction.
Results
Paired sample analysis showed statistically higher PTEN methylation levels in FFPE tumor tissue samples compared to non-cancerous tissue samples ($P=$ 0,016). Plasma PTEN methylation levels were compared before and after PTC surgery. Significantly lower levels of PTEN methylation were found in samples collected after surgery compared to samples collected before surgery ($P=$ 0,031).
Conclusion
PTEN methylation level changes may be a promising minimal invasive biomarker in predicting PTC prognosis and diagnosing PTC.

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EP966

Bone metastases of differentiated thyroid cancer: characteristics and prognostic factors in a multicenter series

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Objective
To describe the characteristics, survival and prognostic factors of a cohort of patients with bone metastases (BM) of differentiated thyroid carcinoma (DTC).
Methods
Multicenter retrospective observational study. Patients diagnosed with DTC and BM between 1980-2021 were included. A Cox regression was performed to study prognostic factors for 5- and 10-year survival. Kaplan-Meier and log-rank tests were performed for survival analysis and comparison between groups.
Results
$n=63$. Follow-up = 35(15-68)months. 30(48.4%) presented with BM at the initial DTC evaluation. 38(60.3%) had papillary variant. 32(50.8%) presented multiple BM. The most frequent location was the spine (60.3%). Other metastases were present in 77.8%, mainly pulmonary (69.8%). 54(85.9%) received treatment with I131, with BM uptake in 31(49.2%). 25(39.7%) received treatment with multikinase inhibitors. 34(54%) presented skeletal related events. 34(54%) died. 5- and 10-year survival was 42.4% and 20.4% respectively. Significant prognostic factors in multivariate analysis were the presence of N1 (HR 2.916 (95% CI 1.013-8.391);$P=0.047$) and treatment with I131 (HR 0.214 (95% CI 0.069-0.665);$P=0.008$) at 5 years; and the presence of other metastases (HR 6.844 (95% CI 1.017-46.05);$P=0.048$) and treatment with I131 (HR 0.23 (95% CI 0.058-0.913);$P=0.037$) at 10 years.
Conclusions
Our study reflects the management of patients with BM of DTC in real clinical practice in several centers in southern Spain. The use of antiresorptive drugs was lower than recommended based on current evidence on their preventive role in SRE. Overall survival at 5 and 10 years was lower in patients who were not treated with I131, had nodal involvement and/or had other metastases.

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EP967

The role of thyroid peroxidase antibodies on the risk of thyroid cancer: a systematic review and meta-analysis of surgical cohort studies

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Introduction
Hashimoto's thyroiditis raises the risk for thyroid cancer (TC) in surgical series, but the role of thyroid peroxidase antibodies (TPO) remains controversial in that regard. We designed the present study to evaluate the effect of preoperative TPO titers in the risk of DTC.
Methods
A comprehensive search was conducted in PubMed, CENTRAand Scopus databases in November 2021 for the terms "thyroid cancer" and "TPO" or "peroxidase antibodies". We characterized the differential risk found in patients with high titers of TPO (TPO+), as compared to those with low or undetectable titers (TPO-) with regard to TC. Data are expressed as odds ratio (OR) with 95% confidence interval (CI).
Results
We retrieved and reviewed 408 records; 22 retrospective cohort studies (2006-2021) from 7 countries and $n=30,077$ subjects, fulfilled the eligibility criteria: 15 studies in East Asia with $n=24,096$ subjects and 7 studies in the Western world with $n=5981$ subjects (19.9%)]. These comprised $n=17,374$ subjects with benign disease and $n=12,703$ with TC. The reference used for TPO+ was 23.6 ± 18.8 (Range 5.1-50.0 IU/ml); $n=6,105$ patients were TPO+ and $n=22,882$ were TPO-. TC was present in $n=2,817$ TPO+ patients (46,14%) and $n=9,122$ TPO- patients (39,87%), RR 1.31 (1.24 - 1.39, $P<0.0001$). A high titer of TPO was associated with increased risk for DTC in Asian cohorts, [OR 1.21 (1.13-1.29, $P<0.0001$)] and Western world alike, [OR 1.91 (1.66-2.21), $P<0.0001$]; That risk was statistically significantly higher in the Western world cohorts as compared to east Asia cohorts OR 1.65 (1.44-1.89), $P<0.0001$.
Conclusions
Thyroid peroxidase antibodies are an integral part of Hashimoto's thyroiditis, which is a well characterized risk factor for thyroid cancer and seem to increase that risk as well. That effect seems significantly higher in the Western world, as compared to the East Asia region. Further studies are needed to characterize the effects of the immune response, with regard to thyroid cancer risk.

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EP968

Benign and Malignant Thyroglossal Duct Cyst Remnants: Systematic Review and Case Series of 1842 Surgical Cases

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Introduction
Thyroglossal duct (TGD) carcinoma is an uncommon entity, diagnosed in patients undergoing evaluation of the neck for midline swelling, or incidentally after removal of a TGD cyst. Despite the presence of multiple publications on the topic, no systematic characterization of these tumors has been performed to date.
Methods
We performed a systematic search for the term "Thyroglossal duct" in Pubmed, Embase and Cochrane databases on December 1, 2021 and retrieved 1229 records. We excluded articles other than case reports or case series, and those written in languages other than English, Italian, French or Spanish.
Results
We incorporated data from 366 manuscripts, comprising 1202 patients operated for TGD disease. Out of these, $n=550$ cancers were identified, consisting of $n=475$ (86.4%) Papillary carcinomas (PTC), $n=8$ Follicular carcinomas (FTC) (1.5%), $n=5$ Hürthle cell carcinomas (HCC) (0.9%), $n=27$ Squamous cell carcinomas (SCC) (4.9%), $n=2$ poorly differentiated/anaplastic thyroid carcinomas (ATC) (0.4%), $n=1$ Adeno-SCC (0.18%), $n=1$ Adenocarcinoma (0.18%), $n=12$ synchronous PTC/FTC (2.2%), $n=1$ synchronous PTC/SCC (0.18%) and $n=18$ of unclear histological diagnosis (4.75%). $n=173$ patients were males and $n=273$ were females; gender was not available in $n=104$ cases. Mean cancer size was 1.3 ± 1.3 cm (range 0.01-7.0 cm); 49.6% were microcarcinomas (<1 cm). Lymph node involvement was present in $n=62/243$ (25.3%). Distant metastasis was present in $n=4$ patients (0.7%).
Conclusions
TGD remnant cancers include various tumors, with histology and features of aggressive behavior similar to what we see in thyroid cancer cases. More research is needed to better understand the mechanisms of tumorigenesis in the TGD.

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EP969

Hashimoto's encephalopathy: a case report

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Introduction
Hashimoto's encephalopathy (HE) is characterised by the combination of clinical signs of encephalitis and autoimmune thyroiditis with elevated levels of antithyroid antibodies (ATA). It is a rare condition and its etiopathogenesis is still poorly understood.
Observation
we present a 33-year-old female patient who was hospitalized for gait disorders. The diagnosis of a chronic cerebellar syndrome related to Hashimoto's encephalitis was retained in view of an elevated TSH level and positive ATA, but the patient was clinically euthyroid. A series of investigations was performed: a cervical ultrasound scan showing a diffuse multi-micronodular goiter. A cerebral magnetic resonance imaging showed a cerebellar atrophy without focal or confluent white matter hyperintensities. A lumbar puncture was performed, showing no hyperproteinorrachia or pleocytosis. The electroencephalogram was normal. Other causes such as tumoural, toxic, malformative and degenerative were ruled out.
Discussion/Conclusion
HE is a rare entity, which was first described in 1966. It is characterised by aspecific neurological and/or psychiatric symptoms. Biologically, it is associated with an increase in ATA in the serum and sometimes in the cerebrospinal fluid of affected patients. The pathogenesis of HE is unknown. The role of ATA is a matter of debate. Indeed, several studies have shown that anti-thyroperoxidase antibodies have a high prevalence in asymptomatic individuals. This entity is usually very sensitive to corticosteroid therapy. It is a diagnosis by exclusion.

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EP970

Thyroid pathology in patients with familial adenomatous polyposis

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Introduction
Familial Adenomatous Polyposis (FAP) syndrome is an autosomal dominant disorder associated with a high risk of multiple intestinal and extraintestinal cancers. They develop hundreds or thousands of adenomas in the rectum and colon during the second decade of life that. If they are not identified and treated, almost all patients develop colorectal cancer (CRC) and die by the age of 40-50 years. Thyroid carcinoma is a FAP manifestation with an unknown reported higher risk with an approximate prevalence of 1-2%. We sought to define the prevalence of t thyroid pathology, defined as autoimmunity, nodularity, and carcinoma.
Materials and methods
Prospective study, selecting 17 living patients diagnosed and registered with APC mutations under follow-up from the Digestive Department of the Hospital Universitario de Navarra (HUN) with current or past follow-up in the Endocrinology Department. Radiological tests, clinical, and analytical variables were analyzed.
Results
The study population included 12 men (64.7%) and 5 women (35.3%), with a mean age of 47 years. The median age at diagnosis of FAP was 28 years, with a mean follow-up time of 16 years. All patients underwent thyroid ultrasound examination and blood tests with the determination of thyroid autoimmunity. The prevalence of nodular pathology was 58.8% (10/17), of which 7 had single nodules and 3 had multinodular goiters. Of the 10 patients with nodular pathology, 5 had nodules >1 cm (29.4% of the total sample). Of these, 4 had indications for cytologic study. The result of the cytologic study was Bethesda II in 3 cases and Bethesda IV in one, so surgical treatment was necessary. The anatomopathological study was follicular adenoma. No malignancy was found in the sample. The overall prevalence of autoimmunity is 31.25% (5/16). Of the 5 patients with thyroid autoimmunity: 2 present thyroid peroxidase antibodies (40%), 2 thyroglobulin antibodies (40%), and 1 patient both (20%).
Conclusion
The prevalence of thyroid nodularity in the sample of patients with FAP is above that described in the general population. Probably the small number of patients in the sample has conditioned the non-detection of thyroid carcinoma.

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EP971

Thyroid calcifications: tragedy or stability

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Thyroid calcifications are a difficult problem to interpret. The deposition of calcium salt crystals often indicates profound morphological changes, cell death, their rearrangement and dedifferentiation. The calcifications are not guaranteed markers of any process. There is also no data on the effect calcifications on the development of a process in the thyroid. The analysis of 67 thyroid nodules, in wich calcifications were detected during ultrasound. Macrocalcifications were detected in 44 cases. They were ring-shaped, lumpy, amorphous, and had an acoustic shadow, the density of which depended on the sizes of the calcifications. Macrocalcifications were clearly detected during clinical examination and surgery in 35 patients. In this cases the biopsy was difficult, since calcifications was an obstacle to the needle, and the acoustic shadow does not allow registering the position of the needle tip. The 13 patients with coarse calcifications had a wide acoustic shadow covering a large volume of the nodules, which did not allow to determine their sizes and the echostructure of the central part. Microcalcifications were detected in 19 cases. The results of the biopsy: 47 patients had thyroid tumors (39 – cancer, 8 – adenomas), 20 – nodular colloidal goiter. Factor analysis revealed that in the group with macrocalcifications, tumor were detected in 59,1%, colloidal goiter in 36,4%. In the group with microcalcifications, tumors were detected in 89,5%, and colloidal goiter in 10,5%. The analysis also found that the detection by ultrasound of a combination of signs of nodules such as hypoechogenicity, blurred contours and "height more than width" (TI-RADS4-5) with a high probability indicates of a tumor and the need for biopsy. The detection of macrocalcifications, a liquid component, Halo rim, and reduced peripheral blood flow in the nodules is more typical for colloidal goiter. However, the presence of calcifications causes high rigidity of such nodules during elastography, which translates these cases into the TI-RADS4 group, in which a biopsy is absolutely indicated. In the group of tumors, macrocalcifications were detected in 55,3%, and microcalcifications in 36,2%. In colloidal goiter, macrocalcifications were detected in 80,0%, and microcalcificatoins in 10,0%. It was also found that the presence of calcifications does not affect the functional

activity of the thyroid. Based on this, we can say that the presence of microcalcifications, along with reduced echogenicity and fuzzy contours of the nodules, is one of the key signs of a thyroid tumor. Colloidal goiter is more characterized by ring-shaped and lumpy macrocalcifications.

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EP972

Paraneoplastic Hyperthyroidism in an Adult with Choriocarcinoma – A Case Report

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Introduction

Hyperthyroidism is an endocrine condition with multiple causes. Paraneoplastic hyperthyroidism due to marked overproduction of human chorionic gonadotropin (hCG) by choriocarcinoma is a rare diagnosis, which results from the homology of the alpha subunit of hCG to TSH.

Clinical case

A 33-year-old man, with a history of cryptorchidism and orchidopexy in infancy and a euthyroid thyroid nodule, presented with nausea, constipation, and abdominal pain. Computed tomography showed a retroperitoneal mass with 90x77x72 mm and multiple bilateral pulmonary nodules. Laboratory data revealed pancytopenia with neutropenia and hCG levels of 144,690 (<2.5) mUI/ml, and testicular ultrasound was normal. He was admitted with a presumptive diagnosis of extragonadal choriocarcinoma with pulmonary metastases and was started on chemotherapy and corticotherapy. Approximately a week later, the patient presented with respiratory insufficiency and hemoptoic cough likely in the context of haemorrhage from the pulmonary metastasis. He was admitted to the intensive care unit for ventilatory support, requiring an increase in corticotherapy dose. On the ninth day of chemotherapy, laboratory data showed maximum hCG levels of 590,399 mUI/ml. Due to the thyroid function compatible with hyperthyroidism [FT4 7.77 (0.80-1.67) ng/dl, FT3 18.5 (2.00-4.40) pg/mand TSH <0.005 (0.270-4.200) uUI/ml], the treatment with methimazole was started. Later results showed negative anti-TSH receptor, anti-thyroid peroxidase and anti-thyroglobulin antibodies. The patient continued treatment, with a favorable response: on the twenty-first day of chemotherapy, hCG levels dropped to 25,656 mUI/ml, pancytopenia and neutropenia improved, and thyroid function showed FT4 of 2.47 ng/dl and FT3 2.58 pg/ml. Approximately 3 months later, the patient is still on chemotherapy and methimazole, with improved thyroid function [FT4 1.20 (0.80-1.67) ng/dl, FT3 3.15 (2.00-4.40) pg/ml and TSH <0.215 (0.270-4.200) uUI/ml] and significantly lower hCG levels [58.9 (<2.5) mUI/ml].

Conclusion

The treatment of paraneoplastic hyperthyroidism due to hCG is directed against the tumor, however antithyroid medication is a useful adjunctive therapy in a presence of frank and prolonged hyperthyroidism. Chemotherapy, in an initial phase, can cause an even more marked increase in hCG levels, as seen in this case. Since symptoms of hyperthyroidism overlap with those of metastatic disease, is important to evaluate thyroid function in addition to the hCG value.

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EP973

Malignancy rates for Bethesda III and IV thyroid nodules in a tertiary referral hospital

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Background

Thyroid nodules are one of the most common clinical entities in Endocrinology practice. Fine needle aspiration (FNA) and the 2017 Bethesda System for Reporting Thyroid Cytopathology have been proved to be an effective tool to identify malignancy risk and guide surgical decision-making. However, thyroid nodules classified as Bethesda (BTH) III and IV remain a challenge, considering the varying risk of malignancy (ROM) found in different papers. The aim of this study is to determine the ROM in BTH III and IV nodules, and its possible correlation with several demographic factors.

Material and methods

Single-centre, retrospective study. Between March 2020 and August 2022, 61 patients with a FNA initially categorized as BTH III or IV underwent thyroid surgery (total or hemi-thyroidectomy). Data included demographic characteristics, FNA cytology result, presence of multinodular goitre (MNG) or solitary nodule (SN), type of thyroidectomy and pathologic diagnosis. Our ROM calculations were compared to the median ROM described in the BTH 2017 Statistics. A p-value less than 0.05 was considered statistically significant.

Results

48 (78.6%) female and 13 (21.12%) male patients were included in the study. Mean age was 57.3+/-14 years. 5 (8.33%) patients had family history of thyroid disease. 58.33% of the patients had been diagnosed with SN and 43.33% with MNG. 39 FNA reports were compatible with BTH III and 22 with IV. Thyroid cancer cases in the BTH IV group were 40.9%. Surprisingly, this value was higher in the BTH III group (53.8%). ROM calculated in our study was significantly higher than the one proposed in the BTH system report (53.8% vs 18%, IC 95% $P<.001$). There was no significant difference in the ROM for BTH IV. BTH III was significantly correlated with the diagnosis of papillary carcinoma ($P<0,05$), but not with the follicular type. No statistical significance was found between ROM and sex, age, family history of thyroid cancer or presence of SN or MNG.

Conclusions

The obtained ROM in Bethesda category III thyroid nodules in this study is significantly higher than the initially suggested by the Bethesda 2017 consensus. It is comparable to other international cohorts previously reported, but in our study thyroid cancer rates were higher in the BTH III group than in the BTH IV one. Ours is one of the first studies describing these data. Our findings suggest that we might be underestimating the potential for malignancy related to Bethesda III thyroid nodules.

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EP974

The Reactive Oxygen Species Level of Blood Monocytes in Patients with Graves' Disease After Radioiodine Therapy

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Background

Increased production of reactive oxygen species (ROS) and oxidative stress play a significant role in the initiation and persistence of the autoimmune process in Graves' disease (GD)

Aim

To study the ROS level of peripheral blood monocytes in patients with GD after radioactive iodine (RAI).

Materials and Methods

The study included 48 patients with a confirmed diagnosis of GD, from 18 to 65 years (mean 46.42 ± 15.26 years). The hormonal status and functional activity of blood monocytes in patients were studied on the day of RAI and 1, 3 and 6 months after RAI. To measure ROS, spontaneous luminol- and lucigenin-dependent luminescence, luminescence induced by zymosan, were determined using the chemiluminescence method with a BLM-3607 analyzer (MedBioTeh, Krasnoyarsk). The rate of reaction development, the maximum level of ROS, the total ROS were determined.

Results

Before RAI the thyroid status of patients corresponds to subclinical thyrotoxicosis that developed when thyrostatic therapy was canceled: TSH 0.08 mU/l (0.01; 0.45), free T4 17.49 pmol/l (12.88; 21.44), free T3 5.28 pmol/l (4.32; 7.38), 12.80 IU/l (5.77; 26.58). Monitoring of patients reveals normalization of TSH levels, a decrease in free fractions of thyroid hormones. The level of TRAb decreased 6 month after RAI – 1.48 IU/l (0.86; 2.91). A decrease in all parameters of lucigenin-dependent spontaneous chemiluminescence in patients with GD compared to the control was revealed: the time to maximum (Tmax) ($P<0,001$), the maximum luminescence level (Imax) ($P=0,038$) and the total ROS (S) were reduced ($P=0,011$). Differences were determined for all points of observation. There were no statistically differences between the control and patients with GD before RAI in the parameters of luminol-

dependent chemiluminescence of monocytes. After RAI decrease in parameters was found when comparing the controls and patients 1, 3 and 6 months after therapy: in luminol-dependent spontaneous chemiluminescence S was reduced ($P=0,009$, $P=0,018$, $P=0,033$, resp.), in chemiluminescence of the induced by zymosan, Imax ($P=0,005$, $P=0,022$, $P=0,019$ resp.) and S were reduced ($P=0,008$, $P=0,017$, $P=0,019$ resp.).
Conclusion
Decrease in the level of initial and induced primary ROS and the total ROS production in blood monocytes of patients with GD before RAI, compared to the control was revealed, that may be a sign of immunomodulatory and restrictive effects of thiamazole, despite the development of subclinical hyperthyroidism. After RAI, the level of primary and secondary ROS of monocytes decreases, that indicates the immunosuppressive effect of RAI and inhibition of autoimmune process.

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EP975

Long-term observation of thyroid immunity - Experience in a single institution of northeast Japan

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Background
Abnormal thyroid autoimmunity is often experienced in thyroid clinic. Some of them are associated with hyperthyroidism (HY) or chronic thyoiditis (Hashimoto, HA). The abnormality, however, is observed not only in HY or HA, but nodular goiter (NOD), and seems to be associated with various factors; age, visiting periods, residence, ABO blood type or others. We analyzed long-term (more than 16 years) data of patients who live in northeast Japan, if there is any characteristics in thyroid immunity.
Patients and methods
6,578 patients (2007-2022), age 54 ± 16 (3-96); female 83.7%), were examined. Observation period: 7.4 ± 7.1 years (median 5). Nodular goiter was 1,442(solid), cyst(513). HY was 577 and HA was 409. Hormonal assay for Tg, anti-thyroglobulin (aTg), thyroid peroxidase antibody (TPO), anti-TSH receptor antibody (TSH-R) and thyroid stimulating antibody (TS), were performed at their visits. Clinical diagnosis was confirmed by ultrasonography(US) and, if necessary, by fine needle aspiration (FNA); classified 0-5(cancer). Signifiance was determined by Kai2 test or student-t test; $P< 0.05$ significant.
Results
1) Correlation analysis: TPO was correlated with aTg, TSH-R, TS. Negative correlation was found with AGE, and positive correlation with ABO blood type ($A<B<O<AB$; $A=30\%$, $AB=58\%$). aTg was correlated with TPO, but not with TSH-R and TS. TPO positive rate decrease with age (78% in 20-29 years old to16% in 60- years old). 2) Changes of autoimmunity during observation years: TPO positive patients showed decreasing of aTg negative rate with years (46% to 3%), whearas aTg positive patients showed increasing of TPO positive rate (82% to 91%). TSH-R and TS in HY patients showed decreasing with period, but remained positive in 60% of patients through observation period. 3) Autoimmunity in disease: Positive (aTg and TPO) rate in NOD was 29% in solid nodules and 23% in cyst. Positive rate was 86% in HY and 98% in HA. 4) Residece: There was significant difference in local communities; TPO positive rate was 34% (city area) to 45%(fisher man's area).
Conclusion
These data suggest that autoimmunity may reflect patients' life style and genetic back ground. Moreover the immunity seemed long-lasting response in most patients of this area.

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EP976

Zenker diverticulum: an uncommon finding during ultrasound examination of the neck area

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Introduction
Ultrasound examination is the preferred imaging technique for thyroid morphology assessment. Sometimes neck sonography reveals extra-thyroidal pathological formations which may be a cause for diagnostic predicaments. The Zenker diverticulum is a type of esophageal diverticulum, located in a natural area of weakness on the posterior pharyngeal wall. It appears as a structure in close proximity to the left thyroid lobe and can be in some cases misinterpreted as a thyroid, parathyroid or a lymph nodule.
Case report 1
A 42-year old female complaining of cough and dysphagia was referred for a fine-needle aspiration biopsy due to a suspicious finding in the left thyroid lobe. A rounded isoechoic formation with micro-echogenic foci, smooth margins and a thin hypoechoic rim was visualized on the posterior surface of the left thyroid lobe. The finding was suspicious of an esophageal diverticulum. The patient had undergone gastroscopy 3 years earlier and diagnosed with chronic gastritis. The cytological result verified lack of malignancy. Based on ultrasound and clinical suspicion the patient was referred for another endoscopy where a Zenker diverticulum was confirmed.
Case report 2
A 47-year old woman was referred for clinical assessment regarding a lump in the left neck area and dysphagia. She had no comorbidities. During the ultrasound examination a large mass behind the left thyroid lobe and partially behind the right one was visualized. The formation resembled an esophageal enlargement. She was referred to a gastroenterologist and further diagnosed with achalasia.
Discussion and conclusion
The Zenker diverticulum, being in close proximity to the thyroid gland, can in some cases be a cause for misinterpretation. The sonographic appearance of these formations can mimic thyroid nodules. Despite this fact, there are several characteristics, which can be helpful for distinguishing an esophageal diverticulum from thyroid nodules. The typical localization on the posterior surface of the left lobe, the thin hypoechoic rim and the dynamics of the formation when the patient is asked to swallow suggest an esophageal diverticulum, especially when these features are combined. Although not the modality of choice, the ultrasound examination can be of significant importance in discovering esophageal diverticula in the neck area.

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EP977

Covid- associated subacute thyroiditis

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Objectives
The number of reported cases COVID-19 associated subacute thyroiditis (ST) in literature is small thus peculiarities of its clinical features remain the subject of interest. The aim of the review is to share our experience of COVID-19 associated ST.
Materials and Methods
We describe 5 cases of COVID-19 associated ST. SARS-CoV-2 diagnosis was based on the presence of its typical symptoms and real-time polymerase chain reaction on nasopharyngeal swab or by positivity of specific IgG.
Results
ST manifested in 15-28 days after COVID-19. General symptomatology (asthenia and malaise) was recorded in all cases. Neck pain and subfebrile temperature presented in 60% cases, one patient described some discomfort in neck but without pain. Thyroid function tests showed mild thyrotoxicosis in three patients (60%) and two patients were euthyroid (40% cases). The median ESR was 28 (18-36). Thyroid ultrasound showed the typical characteristics (hypoechogenic areas with reduced vascularization) in 100 % cases. Steroid therapy with methylprednisolone was the administered in all case. The euthyroid patient with neck discomfort received non-steroidal anti-inflammatory agents firstly, but after 7-12 days they both represented the negative dynamic and treatment with steroids was initiated. The median dose of methylprednisolone was 24 mg. One of the patient had relapse of the process after steroid withdrawal and needed to be cured repeatedly. The time of active cure with glucocorticoids lasted from 3 to 12 month.
Conclusion
Available literature suggests that forms COVID -19 associated ST are mild and sometimes do not require specific treatment. Our experience showed that the disease had more covert clinical symptoms but long period of duration.

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EP978

Phenotypic and genetic features of familial thyroid dyshormonogenesis in the Tunisian population

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Objective
To describe the phenotypic and molecular characteristics of familial thyroid dyshormonogenesis (FTDH) in the Tunisian population.
Patients and Methods
A retrospective descriptive study including two related (R and K) with high consanguinity whose members are carriers of FTDH. Biological and genetic screening was proposed for all consenting members.
Results
FTDH was identified in 11 patients (8 girls, 3 boys) with a mean age of 4 years and 3 months (range: 1 month-17 years). The family screening revealed 10 other members with hypothyroidism not related to FTDH. At diagnosis, 63.6% of the patients were clinically hypothyroid vs 36.4% with apparent euthyroidism who were diagnosed through the family survey. Mental retardation was detectable in 4 children. Three patients also had sensorineural deafness. Three patients had a homogeneous goiter. Mean TSH and T4 were 24.19 mIU/l and 4.73 pmol/l, respectively. The antithyroid antibodies positivity rate was 18.2%. Substitution therapy (mean dose = 125 mg/d) resulted in euthyroidism in all patients. After a mean follow-up of 11.88 years, three patients required thyroidectomy for compressive and/or nodular goiter. Molecular analysis revealed a single mutation (c.875 C> T) (p.S292F) in the TPO gene with recessive inheritance.
Discussion
FTDH is responsible for 15-20% of congenital hypothyroidism cases that can lead to severe neurosensory complications. In the Tunisian population, the TPO gene mutations are the most frequent and would be amplified by a founder effect in certain regions with high rates of consanguinity and endogamy.
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EP979

Hypothyroidism: A challenging condition

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Introduction
Hypothyroidism can present in a variety of ways, from unexpected abnormal blood results in seemingly asymptomatic patients to those with a multitude of debilitating symptoms. Levothyroxine dose titration is a challenge often faced by physicians. We identified 8 difficult cases which following MDT discussion underwent the Thyroxine Absorption Test (TAT) to gain further clarification (Walker *et al.* 2013).
Aim
To identify if the issue is absorption, patient compliance with medication or true thyroid hormone resistance.
Method
Notes and results of 8 patients with various underlying aetiologies of hypothyroidism (table 1) were retrospectively reviewed over 20 months. All patients were female, age ranging from 27-63 years (mean and median 41.6 and 55.5 years respectively). BMI range of 33-41 kg/m2 (mean 36.8 kg/m2). At the first consultation, 6 patients were on levothyroxine and 2 were on combination levothyroxine and triliothyronine. Triliothyronine was stopped 2 weeks prior to the TAT. As per TAT protocol, thyroxine dose was calculated at 1.6 mg/kg/day x 7 which equated to a range of 1000-1200 mg weekly (mean of 1075 mg). Blood tests were subsequently carried out over 6 hours and 4, 6 and 24 weeks with levothyroxine dose adjusted accordingly.
Conclusion
Patient compliance, rather than absorption, was identified as the main challenge. Thyroid hormone resistance was not identified in this cohort. All patients had a reference range FT4 at some point, either during the TAT or following a period of supervised weekly dosing. General improvements in wellbeing was reported but sample size was insufficient for statistical analysis. Psychological support could potentially benefit this group of patients to improve insight into their condition and thus further impact their wellbeing.

Table 1

Number of Patients	Underlying aetiology of Hypothyroidism
2	Thyroidectomy for Graves
1	Graves treated with I131
2	Thyroidectomy for Ca
1	Thyroidectomy for benign nodules
2	Autoimmune hypothyroid

Table 2: RR = Reference Range

	TSH range	TSH mean	FT4 range	FT4 mean	Levothyroxine weekly dose range in mg	Levothyroxine mean weekly dose range in mg
	(RR 0.27-4.2mU/l)		(RR 12-22pmol/l)			
Pre-TAT	2.2-100	44.4	0.6-11.5	5.2	1050-7000	2975
1 Week Post-TAT	0.04-100	24	2.5-28.1	16.2	1050-7000	2975
4 Weeks Post-TAT	0.01-92.9	28.5	2.4-21.1	12.8	900-1400	1094
24 Weeks Post-TAT	5-35.7	21.9	5.3-19	11.4	875-2100	1360

References
Walker *et al.* (2013) 'A thyroxine absorption test followed by weekly thyroxine administration: a method to assess non-adherence to treatment', *European Journal of Endocrinology*, 168 pp.913-917.
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EP980

Assessment of quality of life indicators of operated and non-operated children with primary hyperparathyroidism in the observed aspect at different times

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Aim
To study tne quality of life of children with primary hyperparathyroidism (PHPT).
Material and methods
90 children with suspected PHPT were examined according to anamnesis, outpatient cards and surgical logs. The children were aged from 3 to 15 years old, who were treated in stationary conditions, and then were observed by us on an outpatient basis. 50 of them were treated surgically (1st group), 40 (2nd group) refused surgery for various reasons and received antiresorptive therapy. Complaints, objective, endocrinological condition of all patients were assessed. The preliminary diagnosis was made on the basis of the obtained clinical data, confirmed by laboratory and instrumental studies. To assess QoL, we used questionnaire of Pas and SF-36. The duration of the study ranged from 1-3-6 months to 1 year in the early postoperative period and 5-10-15 years in the long-term period.
Results
Quality of life indicators in patients with PHPT are significantly lower than in the control group, to a greater extent due to pain, general health, social functioning and vitality ($P < 0.05$). Thus, in patients with PHPT before surgery, a significant violation of both the physical and mental components of the quality of life was established. Further, in the 1st group of patients with surgical treatment, in dynamics after 3 and 6 months, all QoL indicators according to SF-36 were significantly closer to the control group in all domains. In the 2nd group of patients with conservative treatment in dynamics after 3, 6, 12 months and 10 years, all QoL indicators according to SF-36 remained significantly lower than the control group in all domains and did not change significantly. Thus, according to our studies of QoL in patients with PHPT of the compared groups, successful surgical treatment with normalization of the level of parathyroid metabolism contributes to a significant improvement in the quality of life of patients with PHPT of the 1st group already in the early stages after surgery and has a lasting effect in the long-term follow-up period.
Conclusions
The results obtained demonstrate the positive effect of surgical treatment from the patient's point of view and confirm the feasibility of assessing the quality of life both at the decision-making stage when choosing a surgical approach and as part of a comprehensive assessment of the effectiveness of therapy in determining the degree of recovery of various aspects of functioning in patients after surgery.
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EP981

Tuberculous lymphadenitis mimicking nodal metastasis in papillary thyroid carcinoma

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Introduction
The tuberculous lymphadenitis is the most common form of extra-pulmonary tuberculosis. The association with thyroid cancer is rare and can mislead the physician with the lymphadenopathy being considered as metastatic. In an endemic region for tuberculosis such as Tunisia, an adequate preoperative evaluation is crucial to distinguish these two entities and provide the patient with the appropriate treatment.
Material and methods
2 cases of a lymph node tuberculosis associated with a papillary thyroid carcinoma treated in our ENT department.
Patient 1
Is about a 37-year-old patient with no significant pathological history who consulted for left cervical lymphadenopathy that has been evolving for 2 months with a recent weight loss of 5 kg. The clinical examination objectified a lymphadenopathy of the III left territory and a right thyroid nodule. The patient underwent right lobo-isthmectomy with an extemporaneous examination identifying a papillary thyroid carcinoma, hence a thyroid totalization with a central lymph nodes dissection. An additional functional left lymph node dissection identified a lymph node tuberculosis. The definitive pathological examination concluded to a 1.5 cm papillary carcinoma of the right lobe of the thyroid with no lymph node metastasis in the central lymph nodes dissection, and tuberculous lymphadenitis in the left functional lymph node dissection. The patient is currently in complete remission after postoperative radiation therapy and anti-tuberculosis treatment. The current follow-goes up to six years with no metastasis.
Patient 2
Is about a 62-year-old diabetic patient who consulted for a right thyroid nodule. During his right lobo-isthmectomy, the extemporaneous examination identified a papillary carcinoma, hence the totalization of the thyroid with a central lymph nodes dissection. The definitive pathological examination concluded to a papillary carcinoma with no lymph node metastasis but rather a lymph node tuberculosis in the central lymph node dissection. The patient received anti tuberculosis treatment for 6 months and a radioactive iodine treatment and is now doing well. The current follow-up goes up to four years.
Conclusion
In the presence of metastatic cervical lymphadenopathy, and even in the presence of suggestive signs such as necrosis and calcifications, in patients in which a papillary thyroid carcinoma is suspected, a tuberculous lymphadenopathy should be considered as a differential diagnosis and should be carefully researched preoperatively in order to limit surgical complications.

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EP982

Vesicular thyroid carcinoma with retropharyngeal node metastasis: case report

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Purpose
Retropharyngeal lymph nodes metastases from differentiated thyroid carcinoma are extremely rare. The objective of this study was to describe our experience in the management of a vesicular thyroid carcinoma with RPMs.
Case report
We report a case of 60 years old female patient who presented a thyroid goiter with pressure symptoms as well as dysphagia. Initial Serum thyroid stimulating hormone (TSH) rate was normal. The ultrasound thyroid showed a multinodular goiter without any malignancy sign. The patient underwent a total thyroidectomy for compressive symptoms. The final anatomophathological examination had concluded to a vesicular carcinoma of the right thyroid (T3 N0 M0) with a very low extension beyond the thyroid. Radioactive iodine therapy were performed to complete treatment. Six month follow up, the patient presented metastatic cervical lymph nodes in the upper jugular nodes (IIA, IIB) with internal jugular vein thrombosis. We performed a Modified radical neck dissection involving the internal jugular vein. During follow-up, an increased serum thyroglobulin rate was noted although appropriate radioactive iodine therapy. Clinical examination and ultrasonograpgy were unremarkable. A neck and chest CT scan revealed a large right mass of 4 cm in the retropharyngeal space, suggesting a retro-pharyngeal node metastasis with a bone metastasis at the rib. Dramatically, the patient passed away one month after.
Conclusion
Retropharyngeal nodes metastases from differentiated thyroid are rare, although it should be considered at the follow-up of the disease. Because these metastases will be missed by routine ultrasonography of the neck, periodic CT scan or MRI is recommended for follow-up.

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EP983

Role and expression of miRNAs (miRNA 149_5p, miRNA-548c-3p, miRNA 3619-3p) in Papillary thyroid cancer progression and metastasis

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Objective
Papillary thyroid carcinoma (PTC) is themalignantcancer with altered microRNA (miR) changes. miR149-5p and miR-548c-3p participates in multiple processes of tumor development, progression, tumor suppression. Whereas miR-3619-3p plays role to promote cell migration and invasion in PTC. However, the role of miR149, miR-548c-3p, and miR-3619-3p in PTC and the underlying mechanisms remain undefined. Therefore, the present study is aimed to quantify therelative expression of these 3 miR's in tissues and whole blood of PTCpatients to understand the underlying mechanism in metastasis and reoccurrence.
Materials and Methods
miR149, miR-548c-3p, and miR-3619-3pexpression was analyzed in PTC tissue and whole blood by Real-Time quantitative Polymerase Chain Reaction.
Results
Our results indicated that miR-149-5p and miR-548c3p was downregulated and simultaneously, the miR-3619-3p expression was found to be upregulated in the tissues and whole blood of PTC patients. Moreover, downregulation ofmiR-149-5p and miR-548c-3p will help in cell viability, colony formation, cell migration, invasion capacity, upregulation of N-cadherin and vimentin genesin both PTC and whole blood samples. A negative correlation was determined betweenmiR's (miR-149-5p and miR-548c-3p) and miR-3619-3p, hypoxia-inducible factor (HIF) 1α or vascular endothelial growth factor (VEGF) levels, indicating that miR149-5p and miR548c-3p inhibited tumor progression by suppressing the HIF1α-mediated VEGF signalling pathway.
Conclusions
Higher expression miR149-5p and miR-548c-3p could suppress PTC progression by inhibiting the HIF1α-mediated VEGF signalling pathway.
(**Key Words** Thyroid cancer, Papillary thyroid carcinoma (PTC)**, NGS** = Next Generation Sequencing, Genomics; Mutation).

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EP984

Fungal necrotizing otitis externa in diabetic patients

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Introduction
Pseudomonal infection is the most common cause of necrotizing otitis externa (NOE), which typically affects elderly diabetic patients. Fungi are a rare cause of this disease. Fungal NOE can be life-threatening if not recognized and treated promptly.

Objective
The aim of this study is to describe the epidemiology, clinical features, management and evolution after treatment of diabetic patients with fungal NOE.
Methods
This is a retrospective study about 17 diabetic patients diagnosed with fungal otitis externa between 1992 and 2022.
Results
This study is about 11 males and 6 females. The average age of the patients was 69 years (51 – 81 years). All of them had diabetes. Five of them, had terminal chronic renal failure. The symptoms included: otalgia and otorrhea in all cases and facial palsy in 4 cases. Fungi isolated from samples were: Candida albicans (4 cases), Candida glabrata (2 cases), Candida tropicalis (1 case) and Aspergillus flavus (10 cas). There was a case of a simultaneous bacterial infection. CT-scan showed lysis: in the temporal bone (all cases), the carotid canal (1 case), the facial nerve canal (1 case) and the jugular bulb (1 case). One patient had thrombosis in the intrapetrous carotid artery and the internal jugular vein. An extension to the parapharyngeal space was found in 3 cases. An extension to the temporo-mandibular joint was found in 5 cases. Treatment included maintaining euglycemic blood glucose levels and anti-fungal medicines (Fluconazole in 4 cases and Voriconazole in the other cases) for the average of 96 days. After treatment, 13 patients were free of disease, 1 patient had brain ischemia and 3 patient presented with recurrence.
Conclusion
Fungal NOE are known to be more aggressive than bacterial NOE. Aggressive disease, lack of response of NOE to antibacterial drugs or progression despite the use of these drugs should raise the suspicion of a fungal etiology of NOE. The current guidelines are lacking in terms of antifungal of choice and optimum duration of treatment.

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EP985

Surgical Management of Thyroid Differentiated Microcarcinomas

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Background
The management of differentiated microcarcinomas of the thyroid (DMCT) is controversial, and ranges from simple active surveillance to total thyroidectomy with bilateral lymph node dissection and post operative adjuvant therapy. Our purpose was to determine prognostic factors to guide the surgery of DMCT.
Methods
This was a retrospective study conducted from January 2000 to December 2017, involving 122 patients with DMCT who were treated surgically, at the ear nose throat and head and neck surgery and the nuclear medicine departments.
Results
In our population (sex ratio = 0.13), the average age was 46 (range 18 to 84). During the first time of surgery, the extent of the procedure was based on ultrasound and extemporaneous examination results: a non-total thyroidectomy was performed in 10 patients (8%), a total thyroidectomy in 108 patients (89%), and a completion thyroidectomy in 4 patients (3%). The dissection of bilateral central lymph nodes (CLN) was done in 46 patients (38%), of ipsilateral CLN in 2 patients (1.5%), and of bilateral CLN et lateral lymph nodes in 10 patients (8%). After definitive histological examination, a surgical complement was performed in 12 patients (9.8%). At definitive histology examination, a typical thyroid papillary microcarcinoma was observed in 60 patients (49%), a vesicular type of thyroid papillary microcarcinoma in 52 patients (43%), and a thyroid vesicular microcarcinoma in 10 patients (8%). Multifocality was observed in 34 patients (27.9%), an extra-thyroidal extension in 2 patients (1.6%), with a mean tumor size 5.8mm. Histological lymph node involvement was observed in 24 patients (36.4%) among the 66 patients who underwent lymph node dissection. A therapy by I131 was indicated in 100 patients (82%). A complete remission was noted in 76 patients (62.3%). Regional lymph node recurrence was detected in 4 patients (3.2%). No cases of distant metastases or deaths have been reported. The analytical study showed that tumor size and multifocality were statistically significant risk factors for occult lymph node involvement.
Conclusion
The "active surveillance" is retained by several authors as the attitude of choice in case of DMCT without risk factors for locoregional evolution. In the absence of such conditions, surgical treatment remains the gold standard.

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EP986

Thyroid hormone replacement during Ramadan fasting is a real challenge to hypothyroid patients. A systematic review and meta-analysis

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Background
Ramadan is the religious month in which Muslims fast from pre-dawn (suhoor) until sunset (iftar), abstaining from all kinds of food, and liquid. The major change in meal times may be challenging for hypothyroid patients on levothyroxine because levothyroxine has a narrow therapeutic index and should be taken on an empty stomach.
Objective
We aim to compare pre- and post-Ramadan Thyroid function tests of hypothyroid patients taking levothyroxine and to determine the best timing of levothyroxine intake during Ramadan.
Methods
We searched PubMed, Scopus, WOS, Google Scholar, Ovid, Science Direct, Clinical trials.gov, and Cochrane Library for studies published in English investigating the effect of Ramadan fasting on thyroid functions in hypothyroid patients on levothyroxine, and/or comparing different time points of the drug intake. Assessed outcomes were TSH change, Free T4 change, number of patients above reference range of TSH. Subgroups of different time points (Pre-Iftar, Post-Iftar, and Pre-Suhoor) were analyzed separately. The analysis was done by RevMan software. The National Institutes of Health (NIH) quality assessment tools were used according to the study designs.
Results
Twelve studies; 3 RCTs, and 9 observational studies were eligible. All studies compared the same group before and after Ramadan (pre-post study). Ramadan fasting is associated with a statistically significant increase in TSH (MD= -1.07, CI 95% [-1.46, -0.67], $P< 0.00001$). However, no difference was found as regards the number of patients with TSH above the reference range (RR= 0.66, [0.41, 1.08], $P= 0.1$). Also, It didn't reflect on an increase in FT4 (MD= 0.01, [-0.03, 0.06], $P= 0.59$). Our analysis showed that taking the drug at pre-iftar, or post-iftar significantly increases TSH after Ramadan ($P= 0.009$, and 0.01 respectively). Taking the drug before suhoor (0.5 to 1 hour) showed no significant difference (MD= -0.72, [-2.25, 0.81], $P= 0.36$), but the heterogeneity between the studies makes the significance inconclusive.
Conclusion
TSH increases significantly after Ramadan. Choosing an optimal timing is still a challenge, but our analysis suggests that taking the drug before suhoor meal by one hour is the best option. More high quality research is warranted to break this controversy.

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EP987

Risk factors for postoperative complications in total thyroidectomy

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Introduction
Thyroidectomy is a quite common procedure. Major postoperative complications of total thyroidectomy, including recurrent laryngeal nerve injur and hypocalcemia are not infrequent. The purpose of this study was to evaluate the incidence and risk factors of postoperative complications after total thyroidectomy.
Methods
We retrospectively included patients who underwent total thyroidectomy over a period of 6 years. Hypocalcemia was defined as a blood calcium level that was strictly below 2 mmol/l and considered definitive after more than 6 months of vitamin-calcium treatment. Recurrent nerve palsy that persists beyond 12 months was defined as permanent.
Results
This study included 372 patients (87.4% female), of whom 117 underwent central neck dissection. The mean age was 48 years. Histopathological examination revealed one to two resected parathyroid glands in 63 patients (16.9%). Hypocalcemia was transient in 116 cases (31.2%) and permanent in 22 cases (5.9%). We observed 43 cases of recurrent nerve palsy (11.6%) of which 39 were

transient (10.5%) and 4 were definitive (1.1%), 1 case of hematoma (0.3%), 4 cases of cervical abscesses (1.1%), 5 cases of lymphorrhea (1.3%) and 7 cases of keloid scarring (1.9%). On univariate analysis, the risk factors of transient hypocalcemia were parathyroid autotransplantation ($P=$ 0.018), parathyroid gland in the surgical specimen ($P=$ 0.001). Transient and permanent hypocalcemia were significantly associated with longer operative time, central neck dissection and cancer on histopathological examination. Male ($P=$ 0.007), smoking ($P=$ 0.013), and Graves' disease ($P=$ 0.042) were significantly associated with definitive recurrent nerve palsy. On multivariate analysis, the presence of parathyroid gland in the surgical specimen was the risk factor for transient hypocalcemia (OR: 2.09) and Graves' disease for definitive recurrent nerve palsy(OR: 670).
Conclusion
Complications of total thyroidectomy occur in specific circumstances. Involuntary parathyroidectomy and Graves' disease were independent risk factors for transient hypocalcemia and definitive recurrent nerve palsy respectively. Given these risk factors, preventive procedures can be considered to minimize the morbidity of this surgery.

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EP988

Evaluation of the adverse effects of antithyroid drugs in the treatment of Graves' disease

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Introduction
Antithyroid drugs (ATD) are usually the first-line treatment for Graves' disease (GD). It represents an effective treatment with good compliance. This therapeutic modality can be the cause of adverse effects including hematological, cutaneous and hepatic complications. The aim of our study is to evaluate the efficacy of ATD as well as its tolerance in patients with GD.
Methods
It is a retrospective study that included 76 patients, with GD, followed in our department and treated with ATD for at least 2 years. Patients who received ATD to prepare them for radical treatment were eliminated. Remission was defined as the appearance of biological euthyroidism maintained after discontinuation of ATD.
Results
Our study included 29 males (38.2%) and 47 females (61.8%) with a mean age of 33.82 years (8-66 years), The mean duration of treatment was 28.73 months (0.5 - 230 months). Remission was observed in 33 patients (43.4%), with a mean duration of 24.8 months (8-72 months). Relapse was observed in 22 patients (28.9%), 7 cases at the time of degression; 29 cases or 87.8% of the cases having achieved remission; and one case after transition to hypothyroidism despite discontinuation of thyroxine treatment, most likely in the context of Hashitoxicosis. Side effects were observed in 16 patients: one case of agranulocytosis occurring 2 weeks after the Introduction of Basdene*, 6 cases of digestive disorders such as vomiting, 2 cases of hepatic cytolysis, 4 cases of ANCA-positive rash, one case of acute pancreatitis stage A with negative etiological investigation and an improvement upon discontinuation of Basdene*. We noted a case of rapidly progressive ANCA-positive glomerulonephritis in a 50-year-old woman, who presented with hematuria. We also noted a case of segmental and focal hyalinosis in a 15-year-old girl with Graves' disease since the age of 5 and a history of ANCA vasculitis at the age of 7-year-old.
Conclusion
Our results confirm that the rate of durable remission on ATD is relatively low. The possibility of the occurrence of ANCA vasculitis and the potential severity of these vasculitis require special attention to systemic symptoms (rash, hematuria, proteinuria) and the search for ANCA in the presence of such manifestations.

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EP989

Immunological and ultrasound characteristics of different forms of postpartum thyroid dysfunction

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Objective
To assess the immunological and ultrasound (US) characteristic of hypothyroidism and thyrotoxicosis developing during the postpartum period.
Patients and methods
66 women with postpartum thyroid dysfunction (PPTD) (30 with hypothyroidism and 36 with thyrotoxicosis) without history of previous thyroid disorder were included. TRAb positive women were excluded from the study. Clinical evaluation was done, TSH, FT4, FT3, TPOAb, TgAb were measured, ultrasound examination of the thyroid gland was performed.
Results
Women who developed hypothyroidism were of similar age compared to women with thyrotoxicosis (29.83 $\pm$ 4.13 vs 29.72 $\pm$ 4.07 years, $P=0.913$). Women with hypothyroidism had significantly higher frequency of TPOAb positivity ($P=0.038$) compared with those with postpartum thyrotoxicosis. No differences in the presence of TgAb were found. On US examination hypothyroid women had larger thyroid volume ($P=0.029$) and higher grade of thyroid hypoechogenicity ($P=0.004$) compared to women who presented with thyrotoxicosis. In TPOAb positive hypothyroid women the levels of antibodies showed positive correlation with TSH ($P=0.030$) and negative relation with FT4 values ($P=0.028$). In TPOAb positive women with postpartum thyrotoxicosis TPOAb levels had positive correlation with thyroid volume ($P=0.004$), but not with hormonal parameters. In TPOAb negative thyrotoxic women however there was significant positive correlation between thyroid volume and FT4 ($r=0.627$, $P=0.029$) and FT3 ($r=0.822$, $P=0.001$) levels suggesting different stimulatory immune effects.
Conclusion
Hypothyroidism as an initial presentation of PPTD is characterized by more pronounced immunological and ultrasound abnormalities than postpartum thyrotoxicosis resulting in a relatively high risk of permanent thyroid dysfunction. In women with a history of PPTD regular follow up is justified.

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EP990

Relationship between thyroid function and metabolic parameters in healthy premenopausal women

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Objective
To investigate the prevalence and the relation between metabolic syndrome components and TSH values below and above 2.5 mIU/l in euthyroid premenopausal women.
Material and methods
446 women of mean age 30.98 $\pm$ 9.3 (18-51 years) with no history of diabetes or lipid-lowering medications were included in the study. Standard oral glucose tolerance test with insulin measurement was performed, TSH, total cholesterol, HDL, triglycerides were measured, LDL and BMI were calculated. All women had TSH within reference range (0.4-4.2 mIU/l) with no significant medical conditions.
Results
266 women had TSH $<$ 2.5 mIU/l (group 1), while 180 had TSH $\geq$ 2.5 mIU/l (group 2) with no differences between mean age (30.8 $\pm$ 8.9 vs 31.3 $\pm$ 9.9 years, $P=0.554$). Group 2 women had higher frequency of overweight or obesity (OR = 1.553, $P=0.039$), elevated triglycerides (OR = 2.290, $P=0.002$), HOMA index higher than 2.5 (OR = 1.804, $P=0.003$) compared to group 1. Moreover, the levels of total cholesterol (5.03 $\pm$ 1.01 vs 4.82 $\pm$ 0.97 mmol/l, $P=0.036$) and LDL (3.17 $\pm$ 0.91 vs 2.99 $\pm$ 0.84 mmol/l, $P=0.027$) were higher in women with TSH $\geq$ 2.5 mIU/l than in those with TSH $<$ 2.5 mIU/l. After adjustment for age and BMI TSH levels showed weak positive correlations with total cholesterol and LDL cholesterol.
Conclusion
The results of the study confirm the association between thyroid hormones and the components of metabolic syndrome. Even high-normal TSH values in these young otherwise healthy women may lead to increased risk of obesity, insulin resistance and dyslipidemia.

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EP991

Impact of L-thyroxine intake schedule on therapeutic balance during the month of Ramadan in patients followed for hypothyroidism

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Introduction
Hypothyroidism is a chronic pathology, which can have several etiologies and which requires long-term treatment. The modification of meal times during the month of Ramadan which can modify the absorption of L-thyroxine, knowing that it interferes with the taking of meals.
Purpose of the study
Assess the impact of L-thyroxine intake schedule on the therapeutic balance during Ramadan in patients with hypothyroidism.
Materials and methods
This is a prospective study that included all patients followed for hypothyroidism on levothyroxine, including patients followed in thyroid carcinoma consultation, having consulted during the pre-Ramadan 2022 period. All the patients included were in euthyroidism before Ramadan or within the TSH objective for patients operated on for thyroid carcinoma. We divided the patients into three groups according to the schedule for taking the treatment (before Shour, before Ftour and without a fixed schedule) and we evaluated the impact on TSHus 6 weeks after the end of the month of Ramadan. We assessed therapeutic compliance based on the Morisky questionnaire.
Results
We collected 177 patients. The average age is 49.8 years with a female predominance of 67.8%. Peripheral hypothyroidism was present in 64 patients (36.5% of cases) while hypothyroidism secondary to total thyroidectomy was present in 113 patients, i.e. 63.5% of cases including 43 thyroidectomized patients for thyroid carcinoma. During the month of Ramadan, therapeutic compliance was good in 81% of cases, average in 11% and poor in 8% of cases. Among our patients, 55% took the treatment before the fasting meal and 43% took it before the dawn meal and 2% did not have a fixed intake schedule. Post-Ramadan, 83% of patients remained in euthyroidism or within the TSH objective in those followed for carcinoma, 8% in hyperthyroidism and 9% in hypothyroidism with no significant correlation between the first two groups.
Conclusion
The change in the schedule for taking L-thyroxine during the month of Ramadan can affect the hormonal balance as observed in our study, hence the importance of monitoring and specific therapeutic education of patients.

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EP992

The Prevalence of Thyrothyropin Receptor, Cytotoxic T Lymphocyte Antigen-4 and Interleukin-1 Receptor Antagonist Polymorphisms in The Group of Hashimoto Thyroiditis in Turkish Community and their Relationship with Clinical Parameters

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Aim
Hashimoto Thyroiditis (HT); is the most common form of hpothyroidism in iodine-sufficient regions. Both genes and and environmental factors are involved in the immunopathological process of HT. Our aim in this study is to determine the prevalence of Thyrothropin Receptor (TSHR), Cytotoxic T Lypmhocyte Antigen-4 (CTLA-4) and Interleukin-1 Receptor Antagonist (IL-1RN) gene polymorphisms associated with HT in Turkish population and the relationship of genotype characteristics with phenotype.
Method
Patients with HT between the ages of 18-75 and healthy controls were included in this prospectively designed study. Clinical symptoms, iodine status according to the age of 6-15 and last city of residence asked in questionnaire and thyroid ultrasonography (USG) were performed in the participants. Peripheral blood was collected from participants for genetic analysis.
Results
The mean age of 244 patients (220 females,24 males) participating in the study was 40.84 years (min-max:18-75); The average age of 107 controls (91 females,16 males) is 38.37 years (min-max:19-65). In the 6-15 age range, the iodine adequacy of the cities where the patients live was found to be significantly higher than the control group (59.46%vs.41.00%; $P=0.002$). Except for dry skin ($P=0.167$) and weight gain ($P=0.968$), hypothyroidism symptoms and signs were significantly correlated with the disease in the Hashimoto group ($P< 0.05$). All controls were euthyroid. On the other hand 56.97% of the patients were euthyroid, 26% were subclinical hypothyroid, 11.07% were overt hypothyroid and 5.33% were hyperthyroid ($P=<0.001$). No difference was found between the patient and control groups in terms of thyroid volumes in thyroid USG ($P=0.506$). There was no significant difference in TSHR, CTLA-4, IL-1RN polymorphism distributions between HT patients and controls ($P> 0.05$). No association was also found between genotype and clinical parameters of patients with HT except the incidence of hypertension in TSHR GC polymorphism in patients is significant compared to CC and GG ($P=0.007$); The rate of hypertension was higher in IL1RN A3A3 and A2A2 polymorphisms in patients ($P=0.031$) and the incidence of HL was found to be higher in A3A3 and A1A1 polymorphisms ($P=0.003$).
Conclusions
The development of HT is multifactorial. In our study, it has been shown that TSHR, CTLA-4 and IL-1RN do not create a significant predisposition to HT. However, it should be taken into consideration that factors such as the diversity of polymorphisms, ethnic differences and the number of patients may affect the results and studies should be evaluated accordingly.

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EP993

Thyroidectomy as a treatment of graves' disease in children

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Introduction
Graves' disease (GD) accounts for 10%-15% of thyroid disorders in children and adolescents.
Material and Methods
We report the clinical, therapeutic aspects and long-term results of 9 children (< 18 years) who had for Graves' disease, from 2000 to 2021.
Results
The mean age at diagnosis was 15,8 years [9 – 18 years]. Our study included 3 boys and 6 girls. One patient had coeliac disease. The surgery was conducted because of failed 2-year medical therapy in 5 cases and compressive goiter in 4 cases. Total thyroidectomy was performed in all cases. The postoperative course was complicated by transient hypocalcemia in one case. After an average follow-up of 5 years, all patients had control of the disease clinical manifestations including Graves' ophthalmopathy and biological euthyroidism.
Conclusion
The use of antithyroid drugs as the initial treatment option in Graves' disease is well accepted. An average two years remission is achieved in about 30% of children. Otherwise, radio-iodine therapy and surgery are considered as treatment options. Compared to surgery, radioiodine therapy can increase the risk of cancer and cause worsening of Graves' opthalmopathy, especially in children. Therefore, surgery may be a better option.

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EP994

Resistance to thyroid hormone alpha: a case report

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Introduction
Resistance to thyroid hormones (RTH) is a rare syndrome. This condition is caused by gene mutations of thyroid hormone receptors (THR). There are two

types of genes that code THR: THR alpha (THRA) and THR beta (THRB). The RTH alpha is associated with mutations in the THRA gene and is less common than RTH beta [1]. It is challenging to identify patients with RTH alpha because usually they only have mildly abnormal (or even normal) thyroid hormone levels and the severity of clinical features may depend on localization of the particular mutation in THRA [1].

Clinical case

A 38 year-old female patient was admitted to our outpatient clinic with symptoms of mild hypothyroidism (obesity, weakness, constipations, lethargy). 10 years ago she was diagnosed with hypothyroidism (FT4 0.69 ng/dl (normal: 0.8-1.9 ng/dl), TSH 1.89 mlU/ml (normal: 0.4-4.0 mlU/ml)) and levothyroxine (L-T4) was prescribed. Currently the patient was using L-T4 75 mg per day. Phenotypic features of the patient showed short stature (height 161 cm), obesity (BMI 40.12 kg/m^2), coarse facial features, skin tags and puffy hands. The laboratory tests showed low TSH, normal FT4 and high FT3. The ultrasound of the thyroid gland showed no changes. Autoimmune thyroid diseases were excluded. Simultaneously the patient was consulted by a geneticist due to neurological disorders (ataxia, speech disorders, epilepsy). For this, next generation sequencing was performed, incidental findings showed a heterozygous THRA mutation NM_199334.5:c.871G > A. The variant was interpreted as likely pathogenic (as there were no records in GnomAD and very few reports in literature with the same interpretation) [1]. The diagnosis of autosomal dominant hypothyroidism due to THRA mutation was confirmed and the treatment with L-T4 was continued. Subsequently, the same mutation variant was verified for the patients' mother and brother.

Conclusion

Although the mutation of THRA gene causes hypothyroidism, the clinical features are mostly mild and the disease is often left undiagnosed or is diagnosed in adulthood as it was in our case. We recommend that RTH should be suspected for every patient that has unusual clinical and laboratory test changes of thyroid function.

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EP995

Calcitonin Measurement in Needle Washout Fluid After Fine Needle Aspiration As a Complementary Diagnostic Test in Medullary Thyroid Carcinoma

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Introduction

The diagnostic accuracy of fine needle aspiration (FNA) in case of medullary thyroid cancer (MTC) has been less studied than in other thyroid cancers. The complementary measurement of calcitonin in the needle washout fluid after FNA (FNA-Ct) could improve the usefulness of this technique.

Materials and Methods

Description of two cases of patients with thyroid nodules suspicious for MTC in whom FNA-Ct was measured as a complementary diagnostic method.

Results

CASE 1: a 53-year-old man who was referred to our Endocrinology department due to a 1.3 cm right thyroid nodule and a 6 cm left thyroid nodule, with elevated CEA in laboratory tests (11.7 ng/ml). The additional blood calcitonin measurement was also elevated (91.3 pg/ml). FNA was performed on both nodules as well as FNA-Ct measurement. The cytology of the right nodule was categorized as Bethesda III with undetectable FNA-Ct and that of the left nodule was Bethesda V with FNA-Ct of 240 pg/ml (2.6 times more elevated than in blood). Total thyroidectomy with central lymphadenectomy was performed and the histological result was MTC in the left nodule and follicular variant of papillary carcinoma in the right nodule. CASE 2: a 79-year-old woman with a history of rectal adenocarcinoma and chronic kidney disease stage IV who presented a progressive elevation of CEA in laboratory tests, hypermetabolic uptake in the left thyroid lobe on FDG-PET, that corresponded to 1.2 cm nodule. The blood calcitonin measurement was also elevated (332 pg/ml). FNA was performed and the cytological result was categorized as Bethesda III. However, FNA-Ct was 800,000 pg/ml (2409 times more elevated than in blood). Total thyroidectomy with central lymphadenectomy was performed, confirming the diagnosis of MTC in the left nodule.

Conclusions

Although there are no obvious cut-off points, the FNA-Ct measurement showed values in both cases higher than blood levels, reinforcing the diagnostic suspicion of MTC and helping to decide on a more appropriate surgical approach. In neither case had cytology been reported as suggestive of CMT.

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EP996

A case report: non-germinal center type diffuse large B-cell lymphoma in thyroid

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Introduction

The diffuse large B-cell lymphoma (DLBCL) is known as one of the most common lymphoma worldwide with the prevalence of 25 % of all of non-Hodgkin lymphoma cases [1], but it is very rearly observed in thyroid. Around 30 % of Clinical cases of the DLBCL appear from extranodal organs, the prognosis depends on the site of origin [2].

Case

A 18-year-old man was admitted to endocrinologist, complaining with a palpable nodule in the front neck for about 2 months. Patient has never been diagnosed with any thyroid disease before.

Diagnostic tests: Laboratory tests: Euthyroid chronic autoimmune thyroiditis was diagnosed TSH 2.3 (normal range 0.4-3.6) IU/l, FT4 12.2 (9.0-21.07) pmol/l, FT3 5.9 (3.34-5.1) pmol/l, ATPO 823 (0-3.2) kIU/l).

Thyroid ultrasound A hypoechoic, ill-defined margin, calcificated nodule was visible in the left lobe of the thyroid gland (EU-TIRADS 5).

Microscopic examination A core needle biopsy of the left thyroid lobe identified diffuse large B-cell non-germinal center lymphoma as diffused lymphoid infiltration of mitotically active cells with large irregular-contoured *nuclei* and sparse cytoplasm with positive *LCA immunolabeling* and negative MyoD1.

PET/CT scan

A 3.3 x 6.2 x 7.3 cm of polysegmental, *FDG - accumulating* lymphoma mass was observed in the left lobe of the thyroid gland. There were no visible metabolically active lymph nodes, infiltrative changes in the lungs and pathological foci in the bones.

Treatment

Treatment consisting of immunotherapy with Rituximab and immunochemotherapy with regimen R-CHOP was initiated. Patient received Filgrastim and Prednisolone for neutropenia prophylaxis. No complications have been observed.

Conclusion

The prevalence of lymphoma in thyroid is very rear, still the early diagnosis and specific treatment is crucial for proper management of the disease, as non-germinal center type large B-cell lymphoma is usually associated with a higher mortality rate compared to germinal center large B-cell lymphoma [3].

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EP997

Levothyroxine liquid oral substitution as a treatment of refractory hypothyroidism due to gastrointestinal malabsorption

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Introduction
Primary hypothyroidism is a common condition. Its treatment is simple and consists of daily levothyroxine intake. Cases with refractory hypothyroidism despite high doses of levothyroxine were reported. Herein, we report the case of a patient with refractory hypothyroidism secondary to gastrointestinal malabsorption that was improved by L-thyroxine liquid oral substitution.
Observation
A 49-year-old woman was admitted for refractory hypothyroidism. Her past medical history included Graves 'disease treated with radioiodine therapy, asthma, and vitamin d deficiency. The patient was treated with levothyroxine 200 µg/day (2.63 µg/kg/day) with good compliance and regular intake. She presented with persistent symptoms of hypothyroidism and a TSH level of 72 mIU/l (nr: 0.35-4.95). A levothyroxine absorption test was performed by oral administration of 300 µg of levothyroxine (3 solid tablets of 100 µg each). The LT4 absorption rate was 25%, consistent with the diagnosis of malabsorption. A second absorption test was carried out by a concomitant oral administration of 300 µg of levothyroxine and 1 g of vitamin C. The LT4 absorption rate was 3 %. Sublingual administration of levothyroxine was not associated with the increase of FT4. Etiological investigations showed negative celiac disease serology and Helicobacter pylori (HP) gastritis. HP infection was treated but symptoms of hypothyroidism and elevated TSH persisted. The levothyroxine dose was progressively adjusted from 200 µg to 400 µg once a day. Biological tests showed a TSH level of 92.4 mIU/l and a FT4 level lower than 0.42 ng/dl (nr: 0.7-1.5). The patient was put on L-thyroxine in liquid form at a dose of 80 drops per day. Two weeks later, she presented with clinical improvement with a normal FT4 level at 1.14 ng/dl.
Conclusion
Refractory hypothyroidism has a significant impact on patients. It can be caused by several conditions such as poor compliance with levothyroxine therapy, drug interferences, and malabsorption syndrome. Liquid formulations tend to have a better effect on patients with gastritis or those receiving proton pump inhibitors. This is thought to be due to increased dissolution and absorption.

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EP998

Abstract withdrawn

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EP999

Recurrence of Graves disease after 30 years

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Introduction
Graves' disease is an autoimmune disease of the thyroid that manifests as hyperthyroidism, homogeneous goiter and sometimes ophthalmopathy. Medical treatment with synthetic antithyroid drugs restores clinical and biological euthyroidism. However, an apparently successful treatment can be followed by relapse in 40% of cases. We report the case of a patient who presented with a recurrence of Graves' disease after 30 years of remission.
Observation
This is a 62-year-old patient, followed for Graves' disease since the age of 30, treated with carbimazole for 2 years and then obtaining remission with clinical and biological euthyroidism. She presented for consultation for thyrotoxicosis with tachycardia, thermophobia, hand tremors and proptosis. Clinical examination found a homogeneous stage III goiter. The biological evaluation confirms the peripheral hyperthyroidism with a TSH slowed down to 0 mIU/ml and elevated T4L. Thyroid scintigraphy found hyperfixing goiter suggestive of Graves' disease. The patient received treatment with iodine 131 radiation therapy at a dose of 20 mci. It is then supplemented by LT4 with favorable evolution.
Conclusion
The evolution of Graves' disease treated medically remains difficult to predict requiring long-term monitoring given the high risk of recurrence even after several years of remission as the case of our patient.

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EP1000

The relationship between TSHR methylation level and clinicopathological factors in papillary thyroid cancer

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Introduction
Papillary thyroid carcinoma (PTC) is the most common thyroid cancer type. It carries a good prognosis. However, approximately ten percent of cases may present with metastatic disease at initial presentation. Fine needle aspiration biopsy cytology is still the gold standard for diagnosing PTC, but there is a technical limitation. That's why minimally invasive diagnostic test is the subject of research in nowadays.
Our objective
We aimed to explore the *TSHR* methylation level in PTC patient's plasma samples and to compare with clinicopathological factors.
Methods
Study included 68 patients with a histologically confirmed diagnosis of PTC treated at Hospital of Lithuanian University of Health Sciences, Kaunas clinics 2020 - 2021. Peripheral blood samples were collected from patients. DNA methylation level changes of *TSHR* were analyzed by quantitative methylation-sensitive polymerase chain reaction. The total tumor size was calculated as the sum of the diameters of all tumors in PTC multifocal cases. Statistical analyses were performed using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). The results were considered statistically significant at $P < 0.05$.
Results
Average age at diagnosis was 48.19 $\pm$ 14.9 years, there were 8 male patients (11.8%) and 60 female patients (88.2%). We observed that *TSHR* concentration were significantly higher in PTC with greater tumor size (>2 cm) compared to lower (≤ 2 cm) tumor size ($P < 0.001$), lymph node metastasis ($P = 0.01$), lymphovascular invasion ($P = 0.02$), multifocality ($P = 0.013$). A weak positive correlation between the concentration of *TSHR* with the total size of PTC tumors was found ($P = 0.09$, $r = 0.315$). However, there was no correlation between demographic characteristics and histopathological subtypes of PTC.
Conclusion
This study analyzed associations between TSHR promoter methylation level and PTC clinicopathologic features. Our results indicate that TSHR promoter methylation may be useful parameter in assessing disease progression. Further studies are also warranted to expand upon our findings.

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EP1001

Papillary thyroid carcinoma and Graves' disease: a case report

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Introduction:
The occurrence of a thyroid cancer on Graves' disease is rare (0.3 to 16.6%). Most often than not, the type found is a papillary carcinoma and is discovered incidentally. Finding a thyroid nodule within the goiter must always raise suspicion of malignancy.
Material and methods
We report the case of a patient followed for Grave's disease in whom a fortuitous association with differentiated thyroid cancer was discovered on a pathological examination.
Observation
A 51-year-old patient with no significant pathological history was hospitalized for an anterior cervical swelling, associated with clinical signs of hyperthyroidism, meanwhile no signs of compression were found. Physical examination revealed an enlarged thyroid with a 2.5 cm right nodule. The lymph node areas were free. The hormonal assessment revealed a profile of a peripheral hyperthyroidism. The cervical ultrasound revealed a multinodular goiter with thyroid nodules classified EUTIRADS 5 on the right side and EUTIRADS 3 on the left side. A thyroid scan showed bilateral l hypo fixing foci. The treatment was initially based on the administration of synthetic anti-thyroid drugs. The evolution was marked by partial improvement of the clinical and biological hyperthyroidism. The patient underwent a right lobo-isthmectomy with an extemporaneous examination that identified a papillary carcinoma of the thyroid, hence the thyroid totalization with a central lymph nodes dissection. Histological examination revealed a 23 mm papillary carcinoma of the right lobe with one metastatic lymph node alongside with a remodeled thyroid parenchyma compatible with Graves' disease. A complementary radiation therapy (3 courses of 100 mCi) was instituted. The evolution was favorable with no signs of recurrence nor extension. The current follow-up goes up to 6 years.
Conclusion
Diagnosing a patient with Graves' disease should never later on blind the physician on a possible association with a thyroid cancer. The subsequent management is similar to that of differentiated thyroid cancers and the prognosis is usually good enough.

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EP1002

Revealing Distant Metastasis of Differentiated Thyroid Carcinoma: About 4 Cases

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Introduction:
Distant metastases of thyroid tumors are rare. They are mainly of pulmonary (10-15%), bone (9%) and brain (<1%) location. These metastases are more frequent with vesicular (20%) than papillary (3.5%) histological type carcinoma. The aim of our work is to document the clinical and radiological aspects as well as the therapeutic modalities of these entities.
Materials and methods
We report 4 cases of distant metastasis that revealed a differentiated thyroid carcinoma: two cases of pulmonary localization and two cases of bone localization collected at our department of otorhinolaryngology and cervicofacial surgery.
Observations (pulmonary metastasis)
These are two women aged 38 and 45 years who consulted for respiratory symptomatology without palpable thyroid nodules, with the finding of a micronodular miliary on standard chest radiography. A whole-body 131 iodine scan and a chest CT scan were also performed for the second patient, confirming the metastatic nature of the lung involvement. The diagnosis was confirmed on lung biopsy for both patients. Total thyroidectomy with bilateral functional dissection was performed in both cases confirming the presence of multifocal papillary carcinoma. A complement by iratherapy allowed to sterilize the sites in one of the two patients after 6 years, and to decrease the pulmonary iodine fixation for the other patient after 6 months.
Observation (bone metastasis)
This is a 55-year-old woman and a 60-year-old man who consulted for low back pain with motor deficit related to lumbosacral osteolysis and ductal invasion for the woman and neck pain for the man. The biopsy concluded to a metastasis of a vesicular carcinoma of the thyroid in both cases. Further imaging showed multinodular thyroid involvement without adenopathy in both cases. The female patient underwent decompressive radiotherapy. Both patients underwent total thyroidectomy associated with bilateral central curage. The histological examination had confirmed the vesicular type for the female patient and the papillary type for the male patient.
Conclusion
Visceral metastases of differentiated thyroid carcinoma have no clinical or radiological specificity. The metastatic potential remains independent of the size of the thyroid nodule. These metastases are more frequent with the vesicular histological type and have a more reserved prognosis. The presence of a single metastasis should prompt treatment with a carcinological aim.

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EP1003

Safety and Efficacy of Radiofrequency Ablation of Thyroid Nodules. Our Experience With A Cohort of 43 Patients

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Introduction
The majority of current guidelines recommend surgery for benign solid nodules with pressure symptoms or a significant growth. Currently, minimal invasive techniques have emerged such as radiofrequency ablation (RF) which achieve significant volume decrease and many cases, the improvement or disappearance of pressure symptoms.
Results
We describe the efficacy and safety of one single-session of RF in our centre performed in thyroid nodules from 43 patients (8 men) with a mean age of 58,6 ± 13 years. Only nodules with a minimum follow-up of 6 months were included (range 6 months to a maximum of 2 years in 28 cases). Half of the patients had a multinodular goiter and only 3 patients were on previous treatment with antithyroid drugs. Mean plasma thyroid hormone levels were 1.75 ± 1.13 mU/l for TSH 8.7 ± 1.34 pg/ml for T4. The mean nodular volume was 21.6 ± 13.4 ml before the procedure. The indications for RF included: pressure symptoms in 37.2% of patients, nodule growth in 48.8% and both criterion in 14% of cases in patients who refused surgery. After RF, transient minor complications (local pain, bleeding) were registered in 46,8% of cases and one patient presented a major complication consisting in a nodule rupture which resolved spontaneously. During the follow-up, mean volume decreased significantly since the first month (14.1 ± 10.7 ml) achieving a value of 9.9 ± 9.1 ml at the 3rd month; 8.35 ± 7.95 ml at the 6th month; 8.5 ± 8.9 ml at the first-year y 7.7 ± 9,6 ml at the 2nd year. The percentage of ablation success (defined as decrease >50% nodular basal volume) also increased progressively: 25,6% ($n=42$) at the first month, 53,5% ($n=40$) at month 3 and 60,5% ($n=39$) at month 6. Pressure symptoms disappeared in all but one patient. Surgery was needed in 7 cases (16,2%), in half of the cases due to RF failure and subsequent nodule growth.
Conclusion
RF is a safe and effective alternative to surgery in patients with pressure symptoms or significant nodule thyroid growth.

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EP1004

Association Between Metabolic Syndrome Components and Urinary Iodine Concentration

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Iodine is important in both thyroid function and human metabolism. The roles of iodine intake on the metabolic syndrome (MetS) etiology remain controversial.

The aim of this study
Was to investigate the relationship between iodine status and MetS and its components. 371 subjects aged ≥20 years were included.
Materials and methods
The presence of MetS was defined according to the Adult Treatment Panel (ATP) III criteria. The prevalence of MetS and its components were calculated based on the level of urinary iodine concentrations (UICs) using the chi-square method. To further explore whether prevalence was associated with UIC, quadratic and UIC-stratified logistic regression models were used.
Results
As UIC changed, the prevalence of MetS presented as a U-shaped curve, showing a lower prevalence of 18.3% at the UIC level of 150-200 μg/l, whereas the prevalence at the UIC level of below 100 μg/l was 32.6%. After adjusting for age, gender and other confounding factors, iodine status of 150-200 μg/l was a protective factor for MetS [OR = 0.674, 95%CI (0.709-0.932)]. UIC level < 100μg/l was a risk factor for hypertension.
Conclusions
Urinary iodine concentrations in adults are U-shaped associated with MetS and its components. A UIC level of 150-200 μg/l was beneficial to hypertension, hyperglycemia and hypertriglyceridemia. The beneficial effect disappeared when iodine was deficiency (<100μg/l).

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EP1005

Relationship between TSH and metabolic parameters in overweight and obese premenopausal euthyroid women with autoimmune thyroiditis on levothyroxine treatment and healthy women

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Objective
To investigate the relationship between serum thyroid stimulating hormone (TSH) and free thyroxine (FT4) and body mass index (BMI), blood glucose, serum lipids and liver in overweight and obese euthyroid healthy premenopausal women and euthyroid women with autoimmune thyroiditis on levothyroxine replacement therapy.
Patients and methods
The study includes 34 premenopausal women with autoimmune hypothyroidism on stable levothyroxine dose and 129 aged-matched healthy premenopausal women. All women had TSH within reference range (0.4-4.2 mIU/l) and were overweight or obese (BMI 25-40 kg/m^2) without pre-existing diabetes. Fasting blood glucose, ASAT, ALAT, total cholesterol, HDL, triglycerides were measured and LDL was calculated.
Results
Women on levothyroxine had higher levels of TSH (2.55±1.02 vs 2.02±0.89 mIU/l, *P*0.009) and FT4 (11.58±1.63 vs 10.80±1.36 pmol/l, *P*0.007) compared to healthy controls. No differences between BMI and the investigated laboratory parameters were found between treated and healthy women. In women with treated hypothyroidism no correlations between TSH and BMI, blood glucose, lipids and liver enzymes were established. FT4 showed significant negative relation with total (r=-0.547, *P*0.001) and LDL cholesterol (r=-0.553, *P*0;001). In euthyroid control group positive correlation between TSH and BMI was found (r=0.291, *P*0.001). FT4 levels did not affect the investigated parameters.
Conclusion
Obesity, blood glucose and lipids are not associated with TSH levels within the target range in premenopausal women with autoimmune thyroiditis on replacement therapy. In healthy women TSH variations within reference range are associated with higher BMI but do not have significant influence on features associated with high risk of metabolic syndrome.

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EP1006

Severe symptomatic hypercalcaemia associated with thymic hyperplasia and mediastinal lymphadenopathy secondary to Graves' Disease

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Background
Hypercalcaemia of hyperthyroidism via increased bone turnover is not uncommon, however it is usually mild and asymptomatic. Corrected calcium (cCa) concentrations ≥ 3.0mmol/l are seen rarely and tend to be associated with high TSH receptor antibodies concentration. Some of the less well-known effects include thymic hyperplasia (TH) and lymphadenopathy. TH is explained by thyroid hormone acting on thyrotropin receptors in thymic tissue to increase proliferation of thymic epithelial cells and thymic medullary lymphoid follicles. Thyroxine can also have a direct effect on lymph tissue causing lymphadenopathy, splenomegaly and lymphocytosis. Importantly, thymic hyperplasia and lymphadenopathy secondary to thyrotoxicosis are benign and reversible with treatment of hyperthyroidism.
Clinical Case
We present a case of a 79-year-old lady, who was admitted acutely to the Emergency Department with symptomatic hypercalcaemia manifesting as confusion, word-finding difficulty, anorexia and worsening lethargy over a period of 12 weeks. cCa on admission was 3.19 mmol/l (2.2-2.6 mmol/l), ALP 173 U/l (30-130 U/l), PTH was normal at 2.0pmol/l (1.8-6.8 pmol/l). Confusion screen revealed hyperthyroidism with free T4 49.2pmol/l (7.7- 15.1 pmol/l), TSH < 0.01mu/l (0.34-5.6 mu/l). Low magnesium was also noted 0.38mmol/l (0.70-1.0 mmol/l). CT scan to screen for malignancy detected an enlarged thymus with calcifications and mediastinal lymphadenopathy. No malignancy was detected. An enlarged thymus was also noted on scan 5 years prior. Global heterogenous enhancement of the liver and spleen likely perfusional in nature was noted and was attributed to thyrotoxic state. Thyroid stimulating immunoglobulins returned strongly positive at 32.6IU/L (<0.1), confirming Graves' Disease without associated goitre or thyroid eye disease. She was managed with intravenous pamidronate, fluids and started on carbimazole. She developed transient hypocalcaemia (cCa 2.05 mmol/l) and hypophosphatemia on days 8 – 11 post pamidronate reflecting hungry bone syndrome due to rapid cessation of bone resorption. Her calcium normalised by day 11 post pamidronate and was maintained in range with normalisation of thyroid function. Endobronchial ultrasound and lymph node sampling and interval scan was offered to further investigate the lymphadenopathy, but were declined by the patient.
Discussion
This case highlights the importance of thyroid function testing when investigating and managing hypercalcaemia as well as the relationship between thyrotoxicosis, increased organ perfusion and thymic hyperplasia, which is most often benign and reversible with appropriate management of the underlying thyrotoxicosis. While our patient declined lymph node biopsy, her lymphadenopathy was clinically consistent with her thyrotoxicosis in the absence of any other apparent sinister cause and red flags.

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EP1007

Graves' orbitopathy and pretibial myxoedema developed years after thyroidectomy

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Background
Graves' orbitopathy (GO), also known as thyroid eye disease, is an autoimmune condition and is one of the main extrathyroidal manifestations of Graves' disease. GO is relatively rare and usually accompanies the onset or develops soon after the Graves' disease. We present a case of GO that developed 18 years later from total thyroidectomy.
Case report
A 64-year-old men presented at the ophthalmology clinic with one-month history of gradual bilateral vision impairment with inability to walk independently, exophthalmos, pain in the eyes, swelling of eyelids, and excessive tearing. From past medical history, 18 years ago, patient underwent a subtotal thyroidectomy due to Graves' disease. 4 years following surgery, his vision started to deteriorate; however, he has not seen a specialist or done any investigations. 4 years ago, he was diagnosed with cataract in both eyes and underwent surgery. Patient was smoker (30 cigarettes/day), BMI = 21 kg/m2. His only regular medication was for hypertension. Physical examination revealed the presence of pretibial myxoedema on both legs and thyroid acropathy. Ophthalmological examination revealed swelling of periorbital tissue, eyelid retraction, and exophthalmos of both eyes. Clinical activity score (CAS) was 6. Moderate-to-severe and active GO was diagnosed. Laboratory tests were consistent with overt hypothyroidism (TSH = 29μIU/ml, FT4 = 0.56ng/dl) and positive TSH receptor antibody (TRAB) titter (7.11U/l). Cerebral and orbital CT scan was also done, which revealed an infiltration of the orbital fat and enlargement of the extraocular muscles. Neck ultrasound revealed 3 nodules in the thyroid bed. FNA cytology of the dominant nodule (33x26x10mm) was performed, which showed follicular neoplasia. Patient was started on 50 mg levothyroxine, he quitted smoking, and a pulse-therapy with methylprednisolone (cumulative dose 4.5 g) was done. After 12

weeks of pulse-therapy, repeated ophthalmological examination revealed moderate and inactive GO, vision significantly improved, pretibial myxoedema completely resolved, patient's quality of life also significantly improved. Biochemically, he was euthyroid and TRAB decreased to 4.63U/l. Thyroid remnant surgery was recommended, but patient refused to undergo the surgery.
Conclusions
Although GO usually presents soon after the onset of Graves' disease, late presentation can also occur, even after long-standing thyroidectomy. Raising awareness among both patients and clinicians in terms of diagnosing GO in time can reduce the severity of complications and ensure better quality of life for such patients.

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EP1008

Monitoring thyroid function test in patients with growth hormone deficiency, receiving growth hormone replacement therapy

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Introduction
Interaction of growth hormone system with Hypothalamic pituitary axis can be complicated, and the effect of GH treatment on thyroid function is still not completely clear. GH has inhibitory effect on conversion of T4 to reverse T3, while enhancing extrathyroidal conversion of T4 to T3.
Objective
To assess thyroid function test in patients with growth hormone deficiency, receiving growth hormone replacement therapy in Slemani, Kurdistan region of Iraq.
Methodology
A prospective follow up study carried out in Endocrine and Diabetic Center in Slemani from October 2014 to October 2015, on a convenient sample of 54 patients with growth hormone deficiency. The patients were followed up to check thyroid function tests (TSH, T3 and T4) at the end of 1, 3, 6, 9 months of GH replacement therapy.
Results
Mean age of studied patients was 14 ± 3.4 years and males were more than females. There was a significant increase in TSH level after 6 months of treatment with GH ($P = 0.02$). No significant differences were observed in T3 level after 9 months of GH treatment ($P = 0.9$). A significant decrease in T4 level was observed after 9 months treatment with GH ($P = 0.03$).
Conclusions
Thyroid hormone T4 of patients with growth hormone deficiency declined while thyroid stimulating hormones increased after growth hormone replacement therapy.

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EP1009

50 Shades of Graves'

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Introduction:
We present a series of 10 cases of GD presenting with seemingly unrelated symptoms with limited features of thyrotoxicosis, where control of thyroid function tests (TFTs) led to complete normalisation of presenting symptoms. In all cases patients were shown to have Graves disease with thyroid antibodies.
Case series review:
1. 82F with symptomatic hypercalcaemia and thymic hyperplasia on CT. Calcium normalised with standard therapy and remained within range with normalisation of TFTs. Hyperthyroidism could cause hypercalcaemia due to increased osteoclastic activity.
2. 37F with visual blurring due to bilateral papilloedema. Brain MRI excluded tumour and lumbar puncture excluded idiopathic intracranial hypertension. No thyroid eye disease or orbitopathy on MRI. TFTs and papilloedema improved spontaneously, where papilloedema mimicking brain tumour 'pseudotumor cerebri' has been reported with GD.
3. 32M with severe headaches and photophobia. MRI head and venogram confirmed extensive cerebral venous sinus thrombosis. Enlarged thymus and splenomegaly on CT. Thymic hyperplasia and splenomegaly resolved with carbimazole. 4. 51F debilitating headaches with features of increased intracranial pressure. CT head excluded space occupying lesion. Symptoms resolved fully with normalisation of TFTs with carbimazole.
5. 67F with symptoms of parkinsonism. Started carbimazole and Sinemet with symptomatic improvement. Sinemet withdrawn after normalisation of TFTs, with symptoms returning slightly. Case suggests dual pathology (GD + PD), with symptom improvement through normalisation of TFTs. Thyroid hormones can increase dopamine catabolism or alter dopamine receptors' sensitivity.
6. 50F with generalized pruritic urticaria refractory to antihistamines and topical steroids. Rash responded promptly to anti-thyroid treatment. Urticaria possibly due to raised IgE with GD, concurrent chronic idiopathic urticaria (CIU) and rash exacerbation by skin hyperperfusion in thyrotoxicosis.
7. 36F with leg oedema, breathlessness, splenomegaly and renomegaly. Organomegaly and symptoms resolved with control of TFTs.
8. 28F with acute manic psychotic episode requiring sectioning. Commenced risperidone and propylthiouracil with improvement in manic symptoms.
9. 39M with one month history of painful gynaecomastia, fully resolving within 2 months of normalisation of TFTs. Gynaecomastia could present with GD due to raised estradiol concentrations and increased aromatisation of testosterone to oestradiol.
10. 33F with increased abdominal swelling and pain from a large ovarian tumour. Histology revealed struma ovarii. Ovarian struma possibly grew due to TSH receptor stimulation with TRAb similarly to cervical goitre in GD.
Discussion
Variability of GD presentation highlights complex interactions between thyroid hormones, autoimmunity, genetics and biochemical processes, highlighting the need to consider TFT's in a wide range of presenting complaints.

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EP1010

Locoregional and distant recurrences of papillary thyroid carcinoma : A case series of 12 patients

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Introduction
Patients with PTC usually have excellent outcomes with appropriate therapy, while up to 30% of patients present with aggressive disease, including patients with locoregional recurrence and distant metastasis.
The aim
Of this study is to analyze the characteristics of patients with papillary carcinoma of the thyroid with locoregional and distant recurrences.
Résults
We included 12 cases of locoregional and distant recurrence of papillary thyroid carcinoma. 10 of our patients are female and 2 are male with a sex ratio of 1/5. The majority of our female patients are younger than 55 years. The initial surgical treatment consisted of lobo-isthmectomy in one patient, total thyroidectomy in 9 of our patients and thyroidectomy with lymph node dissection in 2 cases. Five of our patients had a tumor size greater than 4 cm, in 3 cases the tumor size was between 2.1 cm and 4 cm, and in 4 patients it was less than 2 cm. In our series we noted multifocality in only one patient. Capsular invasion was observed in 6 patients, representing half of the cases. As for the aggressive histological type, we noted only one case of a patient with the oncocytic variant of papillary carcinoma on anatomical-pathological study. Two of our patients had lymph node metastasis in the cervical region at the time of diagnosis. None of our patients had distant metastasis at the time of diagnosis. In one case the ATA risk stratification of recurrence was in favor of a low recurrence risk. In 3 patients the risk of recurrence was intermediate and in 8 cases the risk of recurrence was high. All our patients received radioiodine therapy, 6 patients had received a single cure of radioiodine therapy, 4 patients had received two cures, only one patient had received 3 cures and one patient had received 4 cures of radioiodine therapy. Only one patient had received 2 lines of targeted therapy: sorafenib and sunitinib. Eight patients had locoregional lymph node recurrence alone, one patient had lymph node and lung metastasis, one case had lymph node and bone recurrence in the right sacroiliac joint. One case had a bone metastasis in the tibia. One case had pulmonary and bone metastases in the femur. During the follow-up period, none of our patients died.
Conclusions
Papillary thyroid carcinoma is an indolent disease, but cases having certain characteristics are likely to show recurrence and even become life-threatening.

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EP1011

Echographic characteristics of thyroid cancers in the Regional Hospital of Malaga

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Introduction
Thyroid cancer is the most common endocrine malignancy, and its incidence is increasing worldwide.
Objective
Our aim is to look at the prevalence of ultrasound features and FNA findings of nodules in patients operated on for thyroid cancer in our hospital.
Material and methods
Cross-sectional observational study of patients operated on for thyroid cancer at the Regional University Hospital between 2018-2021, we collected data on the ultrasound characteristics of the nodules and their classification according to the ultrasound risk scales: ATA and ACR-TIRADS. The analysis has been carried out using the JAMOVI program.
Results
88 patients were included: 60 women and 28 men, mean age: 50.8 years (range 14-86 years), mean TSH 2.47 (SD 2.98), mean diameter of nodules: 25.8mm (SD 15.5), 87.1% are solid and 12.9% solid-cystic, 30.6% have microcalcifications and are ill-defined, borders are irregular in 39.5%, higher than wide in 14.1%. According to the ACR-TIRADS classification: II:1.2%, III:17.6%, IV:28.2% and V:47.1%, according to ATA classification: very low suspicion:1.2%, low suspicion:23.5%, intermediate suspicion:28.2% and high suspicion:47.1%. There is concordance between both echographic risk scales in 77 of the 85 patients (statistically significant correlation $P < 0.05$).
Conclusions
Both the ACR TI-RADS and the ATA risk stratification systems provide a clinically feasible thyroid malignant risk classification, with high thyroid nodule malignant risk diagnostic efficacy.

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EP1012

Papillary microcarcinoma: Diagnosis, treatment and outcomes

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Introduction
Papillary microcarcinoma (PMC), is defined as papillary carcinoma of the thyroid that is less than 10 mm in diameter.
Objective
The purpose of this study is to describe the diagnosis, treatment and outcomes of papillary thyroid microcarcinoma.
Material and Methods
This is a retrospective study including 55 cases of papillary thyroid microcarcinoma treated at our department, from 2000 to 2021.
Results
Our study included 8 men and 47 women. The mean age was 48 years (24-73 years). Three patients had hypothyroidism, 1 patient had hyperthyroidism and 2 patients had a history of loboisthmectomy for benign nodules. No personal history of cervical radiation therapy or family history of thyroid cancer have been noted. The average consultation delay was 14 months. The circumstances of discovery were: lateral cervical lymph node metastases in 5 cases, incidentally discovered by histological examination of the thyroidectomy specimens in 51 cases and ultrasound-guided fine-needle aspiration in 4 cases. The surgical procedure towards the gland was total thyroidectomy in 47 cases, loboisthmectomy in 6 cases and lobectomy in 2 cases (totalization). Central lymph node dissection was performed in 42 cases and 5 patients had lateral lymph node dissection. The postoperative course was complicated by: lymphorrea in 1 case, hematoma in 1 case, transient hypocalcaemia in 5 cases, transient Recurrent Laryngeal Nerve Palsy in 3 cases. The mean size of microcarcinomas was 5 mm (1-10 mm). Microcarcinoma was multifocal in 16 cases, non-encapsulated in 28 cases and with extra thyroid extension in 12 cases. Fifteen patients had central lymph node metastasis and lateral lymph node involvement was noted in 5 cases. None of the patients had distant metastasis. Radioactive iodine has been indicated in 42 cases with a dose ranging from 100 mCi to 400 mCi. Thyroid hormone suppression was indicated in all cases. After a mean follow up of 3 years and 6 months, 2 patients presented a recurrence. Five patients were lost to follow-up.
Conclusion
The incidence of papillary thyroid microcarcinoma is increasing due to the extensive use of ultrasound-guided fine-needle aspiration cytology. However, there is no consensus in the management of the disease.

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EP1013

Ectopic Cervical Thymic Hyperplasia In A Patient Treated For Hodgkin Lymphoma

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Background:
True thymic hyperplasia results from stressful situations such as chemotherapy. It commonly presents as an anterior mediastinal mass; cervical location is exceptional. The aim of this work is to illustrate a case of an incidental ectopic cervical thymic hyperplasia in a patient treated for Hodgkin lymphoma.
Case reprt
Here we report a case of a cervical true thymic hyperplasia in a 12-year-old girl who had a Hodgkin lymphoma treated by radiotherapy and chemotherapy. She was referred to our department for a left cervical mass. The PET scan showed a hypermetabolic adenopathy. Mediastinal MRI was unremarkable. The patient underwent resection of the cervical mass under general anesthesia. Pathological examination confirmed the diagnosis of a true thymic hyperplasia.
Conclusion
Residual ectopic tissue may persist during its migration to its final position in the anterior mediastinum. True thymic hyperplasia may result from chemotherapy for lymphoma in the pediatric population. However, its presence in the cervical region is exceptional. Histological examination is necessary for diagnosis if imaging techniques are unable to rule out malignancy.

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EP1014

A patient with thyroid lymphoma diagnosed during follow-up with benign thyroid nodule

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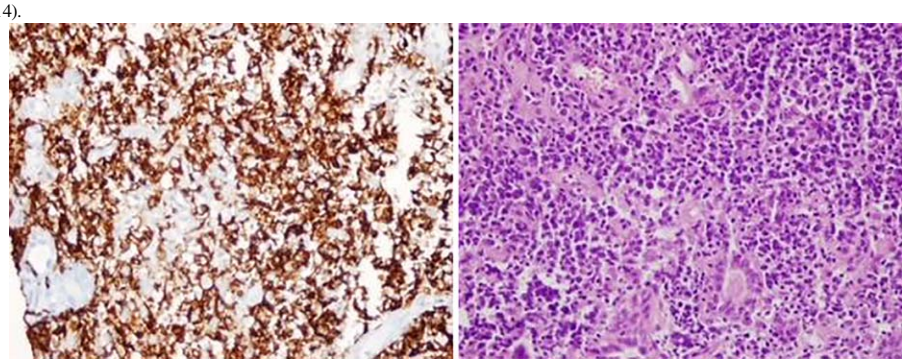
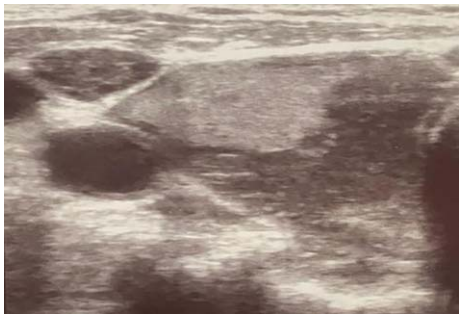
Objectives
Primary thyroid lymphoma constitutes 0.5-5% of all thyroid malignancies. Its incidence is two per million persons. Patients usually present with rapidly growing masses in the thyroid their sixth-seventh decades. The disease is frequently accompanied by chronic Hashimoto's thyroiditis. Most tumors are B-cell derived non-Hodgkin's lymphoma.
Case report
An 84-year-old male patient presented with a palpable swelling in the neck. Ultrasonography revealed heterogeneous hypoechoic thyroid parenchyma (thyroiditis?), a 17x7 mm hyperechoic solid nodule in the right thyroid lobe, 22x9 mm lymph nodes in the right jigular chain. Thyroid antibodies were positive and laboratory tests revealed that the patient was euthyroid. Thyroid fine needle aspiration(FNA) biopsy was performed. The right lobe nodule and lymph node were found to be benign. The patient, who was followed up with benign troid nodule, presented again 6 months later with complaints of rapidly growing mass in the neck, shortness of breath, 10 kg weight loss in the last 1 month and fever. Ultrasonography revealed hypoechoic lesions diffusely infiltrating the parenchyma. Hyperechoic patchy areas and echogenic septa were observed in both lobes except infiltrating areas. Lymphadenopathies of 11x13 mm in the right cervical region and 12x6 mm in the left cervical region were observed. A core needle biopsy (CNB) was performed for definitive diagnosis of suspicious lymph node and thyroid gland and reported as compatible with disseminated large B-cell lymphoma.

Patology: (Abstract EP1014).



Ultrasound: (Abstract EP1014).



Discussion
Thyroid lymphomas are an exceptional finding in patients with thyroid nodules. Given the rarity of this disease, making a prompt diagnosis can be challenging. For instance, FNA cytology, which is the first-line diagnostic test that is performed in patients with thyroid nodules, is often not diagnostic in cases of thyroid lymphomas, with subsequent delay of the start of therapy as occured in our patient. It has been argued that in cases suspicious of thyroid lymphomas, CNB could help to reduce diagnostic surgery and, most importantly, to obtain earlier the diagnosis necessary to start life-saving treatment with multiagent chemotherapy.
Conclusions
We presented this case because it suggests that thyroid FNA biopsy, which is the most commonly used method for troid nodule evaluation, may be insufficient in the diagnosis of thyroid lymphoma. Even if the fine needle aspiration biopsy result is benign, patients should be closely monitored and should be evaluated by CNB or open biopsy when there is high clinical suspicion of malignancy.

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EP1015

What are we going to do with Bethesda IV nodes in future? Do we need molecular testing for all of them?

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Background
Bethesda IV is the most common indication for thyroid surgery. As histological verification is the only 100% certain method of confirming malignancy, surgery remains the gold standard for FN treatment. Most cases of FN malignancy are variants of papillary thyroid cancer that require active surveillance alone in nodules sized less than 2 cm.
Materials
A continuous cohort of 4399 patients who underwent surgery at SPbU_Hospital in the years 2020-2021 with Bethesda IV cytology obtained by FNAB with MG staining.
Results
In 1296 (29,5%) patients malignant thyroid nodules were identified by final histological examination. However, in 406 of those patients (31,3%) malignancy was found in non-punctured minor nodules. Of 980 cases of FN found to be malignant 46% were NIFTP or minimally invasive follicular thyroid cancer and only in 185 (8,8%) cases invasion of at least the nodules' capsule was reported. 39 cases involved an invasion of the gland's capsule (4%). 29 (3,6%) cases had vascular invasion or were suspicious for vascular invasion. 3066 patients had nodules of $\leq$2 cm. Of those patients 578 had malignant nodules (18,9%). In 262 patients (45,3%) the nodules were identified as NIFTP or minimally invasive follicular thyroid cancer. However, the risk of finding cancer with aggressive features in nodules of 2 cm or less was only 0,9%, as compared to 6,4% in nodules $>$2 cm. OR$=$7,4 The risk of finding aggressive cancer in any nodule sized $\leq$2 cm was 0,16%, while that in larger nodules was 1,5%. Most of the malignant nodules were found to be variants of thyroid cancer meeting the criteria for active surveillance. We performed ROC analysis to establish cut off size of FN and the risk of missing an aggressive thyroid cancer (AUC$=$0.84). Cut off nodule diameter of 3 cm showed a sensitivity of 0.8 (0.64 - 0.92), and a specificity of 0.79 (0.78 - 0.81) for the risk of aggressive cancer. For 2 cm sensitivity was 0.84 (0.68 - 0.96), while specificity was 0.6 (0.59 - 0.62). NPV was 0.9984 (0.9971 - 0.9994) for the 3 cm diameter and 0.9983 (0.9966 - 0.9996) for the 2 cm diameter.
Conclusion
It seems that patients with nodules of $\leq$2 cm can safely avoid surgery until the nodules grow in size even if no genetic test is performed. This may also be true for nodules of $\leq$3 cm, should the surveillance criteria for papillary thyroid cancer be expanded.

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EP1016

Hematological changes in patients with Graves disease

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The aim of the study is to identify the frequency of occurrence of various morphological types and various degrees of severity of anemia in patients with Graves disease(GD).
Material and methods
The data of the case histories of 157 patients operated on for GD in 2012 were analyzed. When assessing hematological parameters, two groups were identified: Group 1 - patients with GD with mild anemia ($n=$ 98), age 39.4 $\pm$ 1, 4, men - 41 (41.8%), women - 57 (58.2%) and group 2 - patients with GD with moderate anemia ($n=$ 59), age 41.1 $\pm$ 1.7, men - 11 (18.6%), women - 48 (81.4%). In the clinical analysis of blood, hemoglobin, hematocrit, erythrocyte count and erythrocyte indices MCV, MCH, MCHC were determined.
Results
Microcytic type of anemia was observed more often with moderate severity of anemia (89.8%), and normocytic type of anemia was detected more often with mild anemia (12.2%). Hypochromic and normochromic types of anemia were detected with the same frequency in mild and moderate anemia (hypochromic in 94.9%, normochromic in 5.1%,)
Conclusion
GD is characterized by a high incidence of anemia, more often of mild severity (62.4%), microcytic (88.5%) and hypochromic (94.9%), due to iron deficiency.

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EP1017

Achalasia associated with Grave's disease: case report

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Rationale
Grave's disease (GD) is the most common subtype of autoimmune hyperthyroidism, which can manifest with a variety of extrathyroidal clinical syndromes such as ophthalmopathy, pretibial myxedema (dermopathy), acropathy, cardiomyopathy, and encephalopathy. In very rare instances, GD can also be diagnosed following severe gastrointestinal symptoms such as dysphagia, heartburn, nausea and vomiting. We hereby describe a rare case of GD with digestive symptoms which were later diagnosed as achalasia.
Case presentation
A 26 years old Portuguese woman presented thyrotoxicosis at 2 months of pregnancy. Anti-thyroid stimulating hormone receptor antibody (TSI) was present, and she was diagnosed as GD. Anti-thyroid medication was chosen as the initial treatment for Grave's disease. However, this treatment failed to normalize free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulation hormone (TSH). Throughout pregnancy and three months after delivery, patient had sensation of 'burning' in the anterior cervical region, which extended to the epigastric region. She reported feeling the worst in the morning after waking up noticing an improvement following the ingestion of refrigerated liquids. Daily post prandial vomiting (10 times) became more frequent, with important weight loss (from 76 to 56 kg in the three months after delivery), progressive dysphagia, and global lethargy. No exophtalmus or skin changes were present. Thyroid gland was painless and normal in size. Laboratory assessment showed low serum TSH ($<$ 0,01 mUI/l) and increased both serum FT3 (27,3 pmol/l) and FT4 (63 pmol/l). TSI was still present (4,2 IU/l). A computed tomography scan of the chest and an upper digestive endoscopy were carried out, considering predominant dysphagy-related symptoms, suggestive of esophageal achalasia involving the lower esophageal sphincter. In relation to the significant weight loss, an endoscopic esophageal dilatation was performed in order to improve nutritional status and allow antithyroid drugs treatment to pass through stomach. After dilatation and treatment with anti-thyroid medication, symptoms resolved. Patient recovered her body weight remarkably (56 to a current 64 in one month). FT4, FT3 and TSH normalized after one month of therapy.
Conclusion
We present here a rare case of GD associated with achalasia diagnosed one year after the initial treatment for GD. In case of gastrointestinal symptoms such as dysphagia and vomiting in GD, physicians need to be aware of the possible diagnostic of achalasia as delay in the diagnosis could possibly result in potential harm and/or unnecessary interventions.

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EP1018

Possibilities and priority of ultrasound in thyroid lesions covid-19

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Scientists have studied the direct effect of Civi19 on the pancreas and thyroid gland, in particular, on the development of subacute thyroiditis de Quervian. Our study describes 9 cases of subacute thyroiditis associated with coronavirus infection. Three patients had a mild form of covid19 (positive PCR test result). Subacute thyroiditis was one of the components of multiple organ lesions. Patients had typical manifestations of thyroiditis neck pain, cough, signs of hyperthyroidism. Palpation of the neck revealed local soreness and thickening in the thyroid gland. Laboratory parameters corresponded to the activity of the process (ESR -28,17,35 (respectively), CRP -9,13, 17 (respectively), Ig M level: 4,2, 3,8 and 5,9 (respectively). The main method of examination was ultrasound (separate hypoechoic heterogeneous areas in the thyroid without clear contours). In 4 patients with covid19 of moderate severity, subacute thyroiditis was detected at the rehabilitation stage (all had a negative PCR test, Ig M – 2.2; 1.4; 2.3 and 1.7 (respectively), IgG -34, 121, 231 and 33 (respectively)). It is possible that the disease began at the peak of coronavirus infection. Clinical and laboratory indicators did not indicate a generalized infectious process. The thyroid gland lesions were revealed on the basis of complaints (neck pain) and a specific ultrasound picture (characteristic heterogeneity, hypoechoic zones without clear boundaries with uneven contours according to the type of geographical map with changes in blood flow activity depending on the phase of the process). Two patients with subacute thyroiditis occurred 4 and 5 months after covid19. Before the appearance of subacute thyroiditis, patients had no other viral diseases. The PCR test at the time of treatment was negative. The clinical picture corresponded to subacute thyroiditis: neck pain during swallowing and movement, subfebrility. According to ultrasound dates, there were extensive hypoechoic hypovascular zones in the thyroid with indistinct uneven contours and pronounced hyperplasia of the cervical lymph nodes). Laboratory studies revealed elevated levels of ESR and CRP, titers Ig G -233 and 76 (respectively), Ig M -0.7 and 1.1 (respectively).
Conclusion
Subacute thyroiditis associated with Covid19 can develop into various phases of viral disease. In the diagnosis of thyroiditis associated with covid19, the main diagnostic marker is ultrasound, which requires an assessment of the clinical status. Clinical and laboratory parameters are labile and depend on the stage of the disease. Therefore, all patients with covid19 should undergo thyroid ultrasound at the stages of treatment in order to exclude thyroid damage.

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EP1019

Complications related to necrotizing otitis externa among patients with diabetes

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Introduction
Necrotizing otitis externa is an invasive infection of the external auditory canal and skull base, which typically occurs in older adult patients with diabetes mellitus.
Objective
The purpose of this work is to describe the complications related to necrotizing otitis externa among patients with diabetes.
Methods
This is a retrospective study including 10 diabetic patients with complicated necrotizing otitis externa treated in our ENT department.
Results
Our study included 4 men and 6 women. The mean age was 64 years ranging from 58 to 71 years. The average duration of diabetes follow-up was 10 years. All patients have received oral and local antibiotics before hospitalization. Symptoms were made of otalgia in all patients and otorrhea in 6 patients. Headache and temporo-mandibular joint pain were reported in 2 cases. Fever was observed in 4 patients. Four patients noted ipsilateral facial palsy. Stenosis of external auditory canal was observed in all patients. Pseudomonas Aeruginosa was isolated in 9 cases and Candidada Albicans in one case. CT-scan confirmed the diagnosis of necrotizing otitis externa in all cases. It also showed: an extension to parapharyngeal space in 2 cases, an extension to the rhinopharynx in one case, temporomandibular arthritis in 2 cases, lysis of the skull base in one case, lysis of the facial canal in 2 cases, sigmoid sinus thrombosis in one case and jugular vein thrombosis in 2 cases. MRI was performed in 2 cases showing the extension to parapharyngeal space and to the rhinopharynx. Diabetic control worsened with the onset of the infection in all cases. Nine patients received intravenous anti-pseudomonal medications. Antifungal therapy was conducted in one case. One patient had drainage of the retropharyngeal abscess. Symptoms disappeared in 8 cases and 2 patients had facial palsy as a sequel.
Conclusion
Necrotizing otitis externa is characterized by its aggressive behavior and its difficulty of management, especially among diabetic patients. Early diagnosis, adequate control of diabetes in association with early antibiotic therapy can reduce the morbidity and mortality of this disease.

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EP1020

Case report: Methimazole-induced eosinophilic pleural effusion in a patient recently diagnosed with Graves' disease

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Background
Thionamides are a class of drugs used to control thyrotoxicosis. A wide range of systemic adverse effects have been described, including agranulocytosis, rash, fever, arthralgia, hepatitis and even drug-induced lupus. Besides, there are some uncommon events related to their use, such as pleural effusion (only eight cases have been previously reported). We report a case of methimazole-induced eosinophilic pleural effusion.
Case
Our patient is a 77-year-old female diagnosed with Graves' disease on august 2022, one month after SARS-CoV-2 infection. She started treatment with methimazole 30 mg daily right after the diagnosis. 4 weeks after starting thionamides, the patient developed severe dyspnoea, tachycardia and chest pain, even though thyroid hormones were within normal limits. Chest X-Ray showed extensive right-sided pleural effusion without mediastinal deviation. Blood test showed elevated C-reactive protein and eosinophilia. Thoracentesis result showed exudative fluid with eosinophilia (27% eosinophils); cytology and adenosine deaminase were negative, as well as the result of multiple pleural fluid cultures. She was admitted to our hospital. Blood cultures, IGRA, and autoinmunity tests (antinuclear antibodies, antineutrophil cytoplasmic antibody and antimyeloperoxidase) were performed, all of them came back negative. Total body CT scan didńt show suggestive signs of neoplastic disease. Due to her age and comorbidities, she was not a candidate for pleural biopsy, so our patient was discharged after complete resolution of the pleural effusion, which required three evacuating thoracenteses procedures. Patient kept on using carbimazole. Two months after hospital discharge, we suspected that carbimazole was the potential cause of her pleural effusion, so the drug was discontinued. She was then referred to radio-iodine ablation with subsequent total resolution of the thyrotoxicosis. One month later, chest X-ray showed complete resolution of the pleural effusion without new recurrence.
Conclusion
Although the temporal relationship between the carbimazole use and the development of the effusion was clear, and the most common causes for pleural effusion were excluded, discontinuation of carbimazole was delayed and as a result the patient suffered from several recurrences of the effusion. This case highlights the relevance of keeping in mind the potential adverse events related to the use of anti-thyroid drugs. Some of them, although rare, are associated with severe and even life-threatening consequences. In these cases, definitive treatment alternatives to control the thyrotoxicosis are mandatory to avoid uncontrolled thyroid disease.

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EP1021

A case of acute adrenal insufficiency revealing thyrotoxicosis

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Introduction
The coexistence of hyperthyroidism and adrenal insufficiency in the same individual is a rare clinical condition.A total of 20 cases has been reported in the literature [1]. These two conditions may have the same clinical manifestations such as weight loss, asthenia, and digestive disorders and each one may mask the other. We describe the case of a patient presenting to the emergency department with acute adrenal insufficiency in whom associated hyperthyroidism was discovered.
Case report
A 69-year-old woman presented to the emergency department with asthenia, abdominal pain, vomiting, and a rapidly worsening neurological state leading to mental confusion. In her history, we note a diabetes evolving for 10 years in stop of treatment. T e examination noted an altered general condition with significant weight loss, dehydration without associated hemodynamic or respiratory failure. The presence of exophthalmos and a moderate vascular goiter was noticed. There was no melanoderma. Cardiac tracing revealed atrial fibrillation. The biology showed a venous blood glucose of 8.7 mmol/l, a natremia of 125 mmol/l, a hyperkalemia of 6.29 mmol/l, a renal insufficiency with creatinine of 136 µmol with hyperuremia of 62 mmol/l. So, a cortisolaemia and a TSH were requested and the patient had an emergency hemodialysis session and was put on corticosteroids by intravenous route with clinical and biological improvement. Results of cortisolaemia were of 17.47ug/l and the diagnosis of adrenal insufficiency was retained. TSH was requested, which was reduced to 0.001 mIU/l (0.3-5.6) with an increased FT4 to 64.31pmol/l (7.8-14.8). Anti-TPO antibodies were strongly positive at 602 IU/ml. The patient was transferred to our endocrinology department. The patient was put on synthetic antithyroid drugs, betablockers and oral hydrocortisone therapy.
Discussion
This case illustrates the precipitation of an acute adrenal insufficiency crisis by an unrecognized thyrotoxicosis condition. This can be explained by the fact that thyroid hormones accelerate cortisol metabolism [2]. Thyrotoxicosis increases metabolic demands and induces a state of stress which results in an increased need for cortisol which cannot be procured in case of adrenal insufficiency [2].
Conclusion
It is crucial to consider the diagnosis of adrenal insufficiency in renal insufficiency patients. It is also predijuciable to consider the diagnosis of thyrotoxicosis in some patients having adrenal insufficiency, selected by a well-conducted examination.
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EP1022

Exogenous biotin interference in streptavidin-biotin immunoassays: Interpret results with caution

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A 52-year-old patient with a history of secondary progressive multiple sclerosis was referred to our endocrine vetting service with deranged thyroid function tests (TFTs). Medicines reconciliation demonstrated that the patient was currently on regular fampridine and carbamazepine only. TFTs checked in the community revealed a free T4 of 65.8pmol/l (12.0-22.0pmol/l) with a TSH of 2.03mU/l (0.27-4.20mU/l) and a free T3 of 5pmol/l (3.1-6.8pmol/l). 25-OH vitamin D and vitamin B12 were raised above the reference range, prompting a discussion of whether this patient was taking any over the counter medications. It became apparent that they were taking regular multi-vitamin supplements containing vitamin B7 (biotin) which is known to interfere with the Roche immunoassay. With regards to competitive assays such as free T4, excess biotin competes with the antibody in the reagent for binding sites on streptavidin, causing falsely elevated results. TFTs were subsequently sent to a laboratory in a neighbouring health board and were analysed using the Abbott immunoassay and results returned euthyroid with a free T4 of 13.5pmol/l (9.0-21.0pmol/l) and TSH 2.56mU/l (0.3-5.0mU/l). Biotin is a water-soluble B-complex vitamin that has an important role in metabolism and cell-turnover, and is commonly found in multi-vitamins and dietary supplements. Most multi-vitamins will contain between 40-62.5 mg of biotin, greater than the recommended daily intake of 30 mg. The majority of adults will meet their daily requirements through diet alone, in foods such as eggs, dairy products, vegetables and meat. There have been studies recommending higher biotin doses for patients with demyelinating neurological conditions such as multiple sclerosis. Unfortunately, it is not known what daily dose of biotin our patient was receiving. This case highlights the importance of interpreting deranged thyroid function tests with caution, particularly when the patient is asymptomatic, as was the case here. Similar cases have resulted in patients receiving unnecessary treatment with carbimazole which risks potentially severe side effects. After discussion with our senior biochemists, this assay interference is well documented within the laboratory setting, but is less well known clinically. At the time of writing this case report, Roche are currently working on assays without this interference and we eagerly await the results of this patient's thyroid function when assessed via the updated assay.

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EP1023

Association of Basedow and primary biliary cholangitis : a case report

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Introduction
Primary biliary cholangitis (PBC) is a rare chronic cholestatic liver disease, which is most likely of autoimmune origin. It is often associated with other autoimmune diseases, although it is rarely seen with Basedow.
Observation
We report the case of a 38 years old patient, chronic smoker, who presents clinical and biological hyperthyroidism related to Basedow, treated with synthetic antithyroid

drugs for years with poor compliance and notion of discontinuation of treatment. He was admitted to our department for rapid preparation for radical treatment. The clinical examination showed a patient with alteration of the general state, tachycardic, with frank icterus of cholestatic appearance evolving since 2 months, presence of exophthalmos, and perception of a homogeneous goiter at cervical palpation. In front of the frank icterus, a hepatic assessment was carried out showing a hepatic cytolysis, a hepatic cholestasis and a hepatocellular insufficiency. Abdominal ultrasound was unremarkable. Viral serologies were negative. A liver biopsy was performed, showing a PBC, an esogastro-duodenal fibroscopy was performed, which did not show the presence of esophageal varices. An autoimmune workup was performed to look for associated autoimmune hepatitis, as part of the overlap syndrome is ongoing. For his hepatic problem, the patient was treated with ursodesoxycholic acid with slight improvement of the hepatic balance. Then received a rapid preparation with lugol, bblocker and corticosteroid therapy, and had a total thyroidectomy. The post-operative course was complicated by severe bleeding and hepato-cellular failure, resulting in the patient's death.

Discussion and conclusion

Work has been done to determine the prevalence of autoimmune diseases associated with PBC and to assess their impact on the prognosis of this disease. These diseases were dominated by autoimmune hepatitis and Hashimoto's thyroiditis. The association with Basedow was very rare. PBC is often associated with other autoimmune diseases, which should be routinely screened. Conversely, the search for PBC in patients with other autoimmune diseases is necessary in order to initiate treatment at early stages, thus improving the patient's prognosis.

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EP1024

Assessment of sleep quality in patients with well-controlled primary hypothyroidism

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Introduction

Poorly-controlled hypothyroidism is frequently associated with sleep disorders such as impaired sleep quality and obstructive sleep apnea. The aim of this study was to evaluate the sleep quality in patients with well-controlled primary hypothyroidism.

Methods

This was a single-center, cross-sectional study including 50 patients with well-controlled primary hypothyroidism (TSH level within the normal range: 0.35-4.94 mIU/l) for at least one year. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI). Sleep disturbance was defined by a score greater than 5.

Results

The study included 45 women and 5 men with a mean age of 55 $\pm$ 12.5 years. Hypothyroidism was secondary to Hashimoto's thyroiditis, thyroidectomy, and radioactive iodine treatment in 70%, 16%, and 8% of cases, respectively. Its median duration was 10.4 years. Mean sleep duration was 7.3 $\pm$ 1.8 hours/day, with no significant difference between women and men. The mean PSQI score was 7.6 $\pm$ 4. This score was not correlated with TSH level and levothyroxine dose. Sleep disorders were diagnosed in 34 patients (68%). Seventy-four percent of patients had daytime sleepiness.

Conclusion

Sleep disturbances are common even in patients with well-controlled hypothyroidism. Screening and adequate management of these disorders would improve the quality of life of patients with primary hypothyroidism.

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EP1025

Clinical Significance of Basal and Stimulated Calcitonin Levels in A Case with Obesity Under Liraglutide Treatment

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Background:

Liraglutide is a long-acting GLP-1 receptor (GLP-1R) agonist. GLP-1R is highly expressed in C-cells hyperplasia and in medullary thyroid cancer. We aimed to evaluate calcitonin levels stimulated by calcium test and possible development of C-cell hyperplasia during Liraglutide therapy in a case with obesity.

Case Report

A 50-year-old woman was referred to endocrinology policlinic with complaints of increased appetite and weight gain. There were no history and familial history about thyroidal diseases. In phsical examination, his wieght 92,7 kg, weight 171 cm, body mass index 31,7 kg/m2, waist circumferences 112 cm, blood pressures 114/92 mmHg and pulse rate 76 per minute were detected. The findings of the other systems were unremarkable. For the treatment of obesity, medical nutrition therapy, behavior change therapy and increased physical activity were started. Liraglutide was started when appetite control and weight loss were not sufficient. In third months, basal calcitonin level was 13.6 pg/ml (normal range, $<$ 5 pg/ml), peak calcitonin value was 69.5 pg/ml during calcium stimulation test Thyroid function tests were in normal range, and sonographical evaluation of thyroid gland was shown normal. Liraglutid therapy were stopped because of possible C-cell hyperplasia. The patient was followed up with medical nutrition therapy, behavioral therapy and increased physical activity.

Discussion

Liraglutide leads to variations in both basal calcitonin and stimulated calcitonin. According to our case, the findings suggest the possible induction of the C cells and thus C-cell hyperplasia.

Keywords

Calcitonin, GLP-1R, Liraglutide, obesity

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EP1026

A rare diagnosis of lateral Neck Mass

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Introduction

Ectopic thyroid is characterized by thyroid tissue in a location other than anterior to the upper tracheal rings. The estimated incidence of thyroid ectopia is approximately 1/100,000. The most frequent locations are along the midline from the base of the tongue (90%) to the mediastinum. Ectopic thyroid tissue in the lateral neck is rare. We present a case of an ectopic thyroid gland with an atypical presentation as a lateral neck mass.

Case presentation

A 45 year old woman, with no significant past medical history, who presented with complaints of a painless lateral neck mass for the past 1 year exhibiting rapid progression since the past 3 months. There was no dysphagia, dyspnea or hoarseness of voice. Physical exam was notable for a painless, mobile, 3.5 cm mass, right supraclavicular, rubbery that was not fixed to the overlying skin. There was no cervical lymphadenopathy noted in the left neck or beyond the apparent right supraclavicular neck mass. The thyroid was normal. The neck ultrasound was performed revealing an anechoic liquid mass with a honeycomb structure that was well limited, measuring 42mm and hypervascular on color Doppler. The thyroid bed was scanned and it showed a normal thyroid gland. The CT scan of the neck was in favor of cystic lymphangioma. Her laboratory tests were normal. The mass was surgically removed. The extemporaneous examination of the specimen was benign. The definitive pathological examination indicated a benign thyroid tissue with no evidence of malignancy. Immunohistochemical staining showed the expression of TTF1, Thyroglobulin, Cytokeratin19 yet no expression of Galectin3. The diagnosis of Ectopic thyroid tissue was confirmed.

Conclusion

The presence of thyroid ectopia can create a complicated clinical scenario but can be elucidated through the use of basic radiographic and histologic analyses. Conservative management remains a legitimate option for many patients, with surgical intervention reserved for severe symptoms or malignancy.

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EP1027

Complications of hypothyroidism: a series of 67 cases

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Introduction
Hypothyroidism is a consequence of thyroid hormone deficiency which may be of peripheral or central origin. If hypothyroidism is left untreated, the symptoms progress and lead to life-threatening complications.
Patients and method
Retrospective study of 67 patients with primary hypothyroidism. We determined the different complications associated with hypothyroidism.
Results
We collected 67 patients with overt hypothyroidism. The mean age was 38.76 years. There were 57 women and 10 men. Hashimoto's thyroiditis was the retained etiology in all patients. The mean TSH level was 48.12µUI/l. The mean FT4 level was 7.07 pmol/l. Anti-thyroperoxidase antibodies and anti-thyroglobulin antibodies were positive in 62 and 41 patients respectively. Sixteen patients had complications. The most frequent complications were anaemia and dyslipidaemia in 11 patients each, followed by neuromuscular complications in 8 patients such as myopathy, muscle induration and Hashimoto's encephalitis. Other complications were cardiovascular such as pericarditis in 2 patients, sleep apnea syndrome in one patient and myxedema coma in one patient.
Discussion/Conclusion
Hypothyroidism is the most common endocrine disorder. The complications can be minor or major. Untreated hypothyroidism leads to serious consequences such as myxedema coma which is rare but life-threatening. Treatment is based on L-thyroxine replacement therapy.

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EP1028

Graves' disease and autoimmune bullous dermatosis

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Introduction
Autoimmune bullous dermatoses (ABD) represent a heterogeneous group of AIDs that target different epidermal or subepidermal proteins of the skin and/or mucous membranes. As with any autoimmune disease (AID), it may be associated with other AIDs. We report a case of ABD associated with Graves' disease (GD).
Observation
The ABD was a pemphigus vulgaris (PV) that was diagnosed at the age of 25 years in our patient and she was treated with corticosteroid therapy. After 19 years, in the course of the disease, she developed hyperthyroidism. clinical examination revealed a firm goiter and bilateral exophthalmos. Anti-thyroid antibodies (ATA) were positive as well as TSH receptor antibodies. The diagnosis of GD was retained and she was managed with radioactive iodine therapy with a good clinical course and obtaining biological hypothyroidism after 6 months. our patient also benefited from an HLA typing test which showed : HLA_AB:A1, A white, B17, B40(BW4,BW6).
Discussion/Conclusion
Pemphigus is a rare condition, usually affecting patients aged 50-60 years. Pemphigus vulgaris is the most common form (80% of cases). The association of pemphigus with other AIDs has long been reported and can affect up to 25% of patients. The most frequently reported AITs in association with pemphigus are autoimmune thyroid disease (AITD), rheumatoid arthritis, myasthenia and systemic lupus erythematosus. A higher prevalence of ATAs in patients with pemphigus vulgaris compared to healthy subjects is described (2.5% vs 1.2%). Hashimoto's thyroiditis is the AITD most associated with pemphigus vulgaris according to the literature.

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EP1029

PENDRED syndrome with ectopic thyroid : about a delayed diagnosis

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Pendred syndrome, an autosomal recessive disorder, is the most common syndromal form of hearing loss and involves abnormalities of the cochlea, varying degrees of sensorineural hearing loss and diffuse thyroid enlargement/goiter. We describe a case of a delayed diagnosis of Pendred syndrome. The patient is a 30 years female who had a history of total thyroidectomy 13 years ago. And presented when aged 30 with a cervical abscess of ectopic thyroid under the submaxillary gland. The patient had a hearing loss from the early childhood and she had a 27 year old sister who present the same history of deafness and goiter. It is important to determine an early diagnosis of Pendred syndrome; however, reducing the rate of missed diagnoses and misdiagnoses requires further investigation, thus, it is essential for clinicians to improve their understanding of Pendred syndrome. Hypothyroidism in Pendred syndrome can be–although rarely–present from birth and therefore diagnosed by neonatal screening. We highlight to the general physician the classical features of this syndrome that would aid early diagnosis.
Key-words
goiter, sensorineural deafness, thyroid hormone, Pendred syndrome
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EP1030

Primary Thyroid Lymphoma: Clinical Course vs High Suvmax in Fdg-Pet

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Introduction
Primary thyroid lymphomas (PTL) account for 5% of all thyroid malignancies. Treatment and prognosis depend on tumor subtype. Contrasting with diffuse large B-cell lymphomas (DLBCL), that have an aggressive clinical course and higher maximum standardized uptake value (SUVmax) in Fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET), thyroid extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) usually show an indolent course, lower SUVmax and do not require multimodal treatment. Accurate histological classification remains crucial in PTL approach.
Aim
Raise awareness for the possibility of high captation of FDG in Thyroid MALT Lymphoma (Tml) by presenting a case of TML with SUVmax of 21 in FDG-PET.
Case
A 66-year-old woman presented to the endocrine clinic due to cervical enlargement, dysphagia for solids and dyspnea with thorax anteflexion for the last four months. She denied any other symptoms. A large asymmetric multinodular diving goiter with right tracheal deviation had been firstly documented three years before. Clinically she had thyroid enlargement, multiple palpable nodules, and developed Pemberton sign. Laboratory findings included euthyroid Hashimoto Thyroiditis. Ultrasound guided fine needle aspiration (FNA) cytology of the dominant nodule (EUTIRADS-5) suggested Non-Hodgkin B Lymphoma. Two core biopsies revealed chronic lymphocytic thyroiditis with abundant B cells, suggesting PTL, which was confirmed by clonality analysis. FDG-PET revealed intense uptake exclusively in the thyroid with SUVmax of 21. Considering Ann Harbor staging IE-localized disease, and compressive symptoms, a diagnostic and potentially therapeutic total thyroidectomy was performed, with subsequent symptoms resolution and TML histologic diagnosis.
Discussion and Conclusion
PTL approach relies on accurate tumor classification. In this case, the chronic thyroiditis substract supported TML diagnosis, while the clinical course with recent compressive symptoms and SUVmax of 21 raised discomfort in postponing medical treatment in case it was a DLBCL, or TML with recent B-cells transformation, urging the need for final diagnosis. Total thyroidectomy proved to be both diagnostic and therapeutic. The clinical evolution and higher than expected SUVmax challenged final TML diagnosis.

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EP1031

Combination of recurrent thyroid artery embolization and sorafenib treatment in the management of inoperable papillary thyroid cancer

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Introduction
Thyroid papillary cancer is a solid organ malignancy that can be cured mostly by surgical and radioactive iodine(RAI) therapy. Metastatic disease state and radioactive iodine resistance have led to new treatment searches. In recent years, sorafenib, a tyrosine kinase inhibitor, has been used as a first-line treatment in thyroid papillary cancers that cannot be cured by surgery or radioactive iodine treatment. In addition, the use of thermal ablation and transarterial embolization in the curative or palliative treatment of patients who cannot undergo surgery is becoming increasingly common.
Case Report
A 76-year-old male patient was admitted 2 years ago with a swelling and bleeding wound on his right neck. The biopsy was concluded as papillary thyroid cancer. Right lateral neck dissection + total thyroidectomy was performed to the patient. Since the patient's fistulized mass to the skin invaded the right common carotid artery, the mass was incompletely removed, and then a total of 350 mCi RAI was given in the follow-ups. The patient, who was evaluated in the council for reoperation due to open wound, without distant organ metastasis, was considered inoperable. Right inferior thyroid artery embolization(TAE) was planned for palliation for the patient who had continuous bleeding from his open wound and needed 8-10 dressing changes per day and monthly erythrocyte suspension replacement. In the neck computed tomography was taken 2 months later, a volumetric decrease of 82% was observed, and the amount of bleeding of the patient decreased. The patient was started on sorafenib 2x400 mg, but the dose was reduced to 1x400 mg due to the side effect of thrombocytopenia. In the first year of the follow-up, due to the increase in the amount of bleeding from the wound and the need for erythrocyte suspension, neck computed tomography angiography was performed again, and right superior thyroid artery embolization for palliation was performed 2 more times at 9-month intervals. The follow-up and sorafenib treatment of the patient whose bleeding amount is reduced continues.
Conclusion
TKI's increase the progression-free survival of patients with inoperable and radioactive iodine treatment-resistant thyroid papillary cancer cases. Transarterial embolization reduces the mass size by reducing mass blood supply and can be used as a curative or palliative treatment option.

Laboratory results	Before 1st TAE	2nd onth of 2nd TAE	Before 2nd TAE	2nd month of 2nd TAE
Thyroglobulin (referance:1,6-59 ng/ml)	22	1,21	7,17	3,10
Anti-thyroglobulin (referance:0-115 IU/ml)	13	<10	<10	<10
TSH (referance: 0,27-4,20mIU/l)	0,02	0,01	0,02	0,01

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EP1032

Thyroid cancer yield in patients with Graves' disease

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Background
Thyroid nodules found in patients with Graves' disease have a higher likelihood of being malignant. Management of these association is controversial.
Objectives
To discuss clinical and therapeutic features of this association.
Materials and methods
We report three cases of thyroid cancer occurring in Graves' disease, treated surgically at our department.
Results
There were three patients, aged respectively 19, 20 and 49 years, addressed for surgical management of a Graves' disease resistant to medical treatment. The exam found Homogeneous goitre in all cases, firm and hard nodules in two cases. scintigraphy showed cold nodules and ultrasound suspected malignancy in only one case. *Histopathological* examination concludes to a papillary carcinoma in all cases (from 0,5 to 2,5 cm) including one with Extra thyroid invasion and Metastatic central lymph adenopathy. All patients received a total thyroidectomy and *Radioactive iodine therapy*. One patient had central and lateral neck dissection. *Evolution* was a complete remission in all cases.
Conclusion
Prevalence of thyroid cancer in Graves' patients is 0.4% to 10%. It is explained by the stimulating action of the anti TSH antibodies on adenylcyclase. The characteristics of this association are: higher incidence of papillary carcinoma and multi focality, extra thyroid invasion, lymph node metastasis, loco regional and distant recurrence. Ultrasonography should be used routinely to detect any associated nodule. Fine needle aspiration has an important place in the monitoring of these nodules. Total thyroidectomy with histopathological study is indicated at the slightest sign of malignancy.

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EP1033

Association of papillary and medullary thyroid carcinoma in multiple endocrine neoplasia type 2a

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Introduction
The association of papillary carcinoma with medullary thyroid carcinoma may in rare cases be found in some members of families with multiple endocrine neoplasia type 2a (MEN 2a).
Case Report
A 38-year-old patient with a family history of papillary thyroid carcinoma (PTC), operated for multinodular goiter classified Tirads 4 by total thyroidectomy, the anatomopathological examination concluded to a lobar medullary thyroid carcinoma (MTC) of 20mm and an isthmic PTC of 5mm. Calcitonin was not measured preoperatively and was negative postoperatively. The patient was put on LT4 suppression treatement. The genetic study showed a mutation in exon 10 of the RET gene in favor of MEN 2a. The search for other components of MEN 2a revealed a pheochromocytoma of the left adrenal gland, the patient was referred for surgery and a family genetic study was requested.
Discussion
PTC may be associated with sporadic CMT or CMT in patients with MEN 2a with RET proto-oncogene mutation. In MEN 2a, some germline RET mutations have oncogenic activity on thyroid follicular cells. Nevertheless, this activity remains modest and occurs in specific circumstances explaining the rare occurrence of PTC in this context. This observation underlines the importance of calcitonin determination before surgery in case of thyroid nodules to avoid inappropriate therapeutic management
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EP1034

Papillary Thyroid Cancer is also more common in The Iodine Deficiency area: Evaluation of 2748 Patients

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Thyroid cancer is the most common malignancy of the endocrine system. Papillary thyroid cancer is the most common thyroid malignancy worldwide and has a good prognosis. The prevalence of follicular thyroid cancer in endemic iodine deficiency regions is higher than in regions without iodine deficiency. However, it has been observed that the incidence of follicular thyroid cancer decreases and the incidence of papillary thyroid cancer increases after iodine prophylaxis. The Our study, 2748 patients (2201 females, 547 males) admitted to the Endocrinology Department of Faculty of Medicine/Karadeniz Technical University between January 1993 and June 2018 were diagnosed as thyroid cancer pathologically. In this study, papillary thyroid cancer was the most

common type of thyroid cancer in Trabzon, endemic iodine deficiency region. It was observed that the incidence of thyroid cancer tended to decline after peaking in 2012 according to the years of diagnosis. Of these cases, 2201 (80.1%) were female and 547 (19.9%) were male. Female cases were observed 4 times more. The age range of the cases was 18-89 and the mean age at diagnosis was 48.14 ± 12.5. The mean age of the female cases was 47.5 ± 12.8, and the mean age of the male cases was 51.3 ± 11.9. It was observed that female cases were diagnosed at a younger age than males and it was found to be statistically significant ($P < 0.001$), (Table 9). The cases diagnosed with thyroid cancer histopathologically were divided into 7 diagnostic groups. 1) 2571 Papillary Thyroid Cancer (PTC), 2) 97 Follicular Thyroid Cancer (FTC), 3) 45 Medullary Thyroid Cancer (MTC), 4) 16 Anaplastic thyroid cancer (ATC), 5) 7 Hurthle cell cancer (HTC), 6) 11 Mixed type thyroid cancer (MixedTC) and 7) 1 poorly differentiated carcinoma group (poorly differentiatedTC) (Table 1). PTC was evaluated as two main groups; Those with tumor size less than ≤10 mm were called papillary microcarcinoma. The distribution of 2542 PTC cases with tumor size in our study; 1238 (48.7%) papillary microcarcinoma, 1304 (51.3%) >1 cm PTC. 83.4% (1032/1238) of cases with papillary microcarcinoma were female, 16.6% (206/1238) were male, 78.3% (1021/1304) of cases with PTC > 1 cm were female, % 21.7 (283/1304) of them are male.

	CASES	n: 2748
Age		$P < 0,001$
Mean ± SD	48,1 ± 12,5	
Female	47,5 ± 12,8	
Male	51,3 ± 11,9	
Gender	**%**	
Female	%80,1	2201
Male	%19,9	547
Histopathology	**%**	
PTC	%93,5	2571
FTC	%3,5	97
MTC	%1,6	45
ATC	%0,5	16
HTC	%0,2	7
MixedTC	%0,4	11
Poorly differentiatedTC	%0,03	1

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EP1035

Graves' Disease Hiding Metastatic Papillary Thyroid Carcinoma - case report-

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The coexistence of Graves disease (GD) and thyroid carcinoma used to be considered uncommon, but association between the two is being progressively acknowledged.
Case report
We present the case of a 69-year-old woman with a 10 year history of GD who was referred to our clinic for fatigue, sweating, palpable cervical mass and weight loss. She was treated only in the previous 5 months with block and replace therapy. Laboratory workup at admission showed suppressed TSH (0.0003 µUI/ml), high levels of FT4 (31.08 pmol/l) and T3 (>600 ng/dl), positive TRAb (30.85 UI/l). Thyroid ultrasound revealed a multinodular goiter with two hypoechoic macronodules in the right lobe and isthmus classified as TIRADS 4. Technetium-99m scintigraphy showed multinodular goiter with a cold nodule over the right lobe and fine-needle aspiration citology smears of the isthmic nodule were suggestive of follicular carcinoma oncocytic type. High doses of methimazole (40 mg/day) were required to lower thyroid hormone levels preop, but TSH remained suppressed. Total thyroidectomy along with lateral neck lymph node dissection were performed. Pathology yielded a diagnosis of background of GD with invasive PTC in the isthmic nodule with poorly differentiated areas and metastasis in a right lateral lymph node - pT4bpN1bST4G2R1LV1. Postoperative follow-up revealed high titers of thyroglobulin (>500 ng/ml) and antithyroglobulin antibodies (461.3 UI/ml) with a suppressed TSH off levothyroxine; cervical ultrasound demonstrated a small paratracheal remnant of thyroid tissue and nonspecific lymph nodes laterocervical bilateral. Whole body radioiodine scan after Thyrogen showed significant iodine uptake in the thyroid bed and retrosternally and additional ^{131}I accumulation for both lungs. Patient received 100 mCi ^{131} with a drop in thyroglobulin level. Genetic profiling is pending.
Discussion
Genomic profiling allows personalisation of thyroid cancer therapy based on molecular information. A multi-step model of progression from well to poorly differentiated carcinoma has been proposed which includes 2 types of molecular events comprising 'early' events such as RAS and BRAF mutations and late 'events' as TERT and TP53 mutations. In this case we expect to find 'early' driver events like RAS/BRAF mutations which are the most prevalent in poorly differentiated cancer.
Conclusion
This case outlines the importance of further assessment for underlying malignancy when a nodular thyroid is present on the background of GD and genetic profiling of such malignant nodules to guide second stage therapy in the event of progressive disease after standard therapies.

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EP1036

Formation of a database of relatives of patients of the first degree of kinship operated on for medullary thyroid cancer

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To analyze the data of relatives of first-degree patients operated on for medullary thyroid cancer (MTC), we analyzed the anamnestic data of the database of patients with MTC, formed on the basis of the cancer registry of the Republic of Belarus and medical records of the Republican Thyroid Tumor Center. Further examination of relatives is also performed on the basis of the Republican Center for Thyroid Tumors.
The aim
of the study was to create a database of first-degree relatives of patients operated on for medullary thyroid cancer with identified mutations in the RET proto-oncogene.
Materials and methods
An electronic database was created in the Excel far entering the results of demographic, clinical, morphological, instrumental, laboratory and molecular genetic studies. Rows correspond to each of the study subjects. The columns correspond to the features indicated in the description of the study design.
Results and discussion
The group included 76 (30 men and 47 women, the median age was 43 years) first-degree relatives of patients operated on for MTC, mutations in the RET proto-oncogene were detected in 35 people. The distribution of participants by region varied from 20.0% to 35.0%. A survey, collecting an anamnesis, a clinical examination data with measurement of blood pressure, ultrasound of the thyroid gland of regional lymph nodes was performed. Nodular pathology of the thyroid gland was detected in 58 patients, hyperplasia of the cervical lymph nodes in 62 patients, a combination of nodular goiter and cervical lymphadenopathy was registered in 49 people. Puncture-aspiration biopsy of the thyroid gland (and LU) was performed in 45 patients; the results were benign. In individuals with nodular pathology of uncertain malignancy potential were used calcitonin stimulation test. Taking into account the hereditary factor and with elevated levels of calcitonin, preventive thyroidectomy was performed in 5 cases. Data for hyperplasia of the parathyroid glands were detected in 7 patients, further additional examination was carried out in case of suspected diagnosis of hyperparathyroidism. Computed tomography was performed in 9 patients; data for tumor pathology were not established.
Conclusions
An increase in the level of basal calcitonin and parathyroid hormone was noted in relatives of first-degree patients operated on for MTC with a mutation in the RET proto-oncogene, but without statistical significance of differences ($P = 0.067$ and $P0.120$, respectively). Currently, further analysis and systematization of the results of examinations is being carried out, including the results of molecular genetic testing.

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EP1037

Coexistence of thyroid carcinoma and graves' disease: report of two cases

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Introduction
Graves' disease (GD) is a common autoimmune thyroid disease. The association between GD and thyroid carcinoma (TC) remains controversial. We describe two patients presenting this association.
Case report
Case 1 a 46 years old woman with clinical history of type 2 diabetes, she was diagnosed with Graves' disease and multiple nodules were found in her enlarged thyroid gland by ultrasonography. The patient underwent total thyroidectomy after the achievement of euthyroïdism by medical treatment. Histopathological study demonstrated a papillary thyroid carcinoma without capsular invasion. Case 2 a 36 years old woman, with no known past medical history, the diagnosis of GD was based on the findings of biological hyperthyroidism, thyroid gland enlargement and the presence of TSH receptor antibodies. Total thyroidectomy was performed for methimazole-induced agranulocytosis. Histopathological study demonstrated an 8 mm follicular thyroid carcinoma with massive vascular invasion.
Discussion
GD is treated with antithyroid drugs, radionuclide therapies, and surgery. The common surgical indications for GD include non-responsiveness to medical or radio-ablative therapies, a large goiter with compressive symptoms, and worsening of ophthalmopathy. Several studies have demonstrated both an increased incidence of follicular thyroid cancer in surgical treated Graves' disease patients, with rates varying from as low as 1% to as high as 9% of cases. The mechanisms responsible for the increased thyroid cancer incidence in patients with GD remains to be elucidated. It is thought that thyroid stimulating antibodies may be responsible for this increase. Regarding TC prognosis in GD, it is controversial with some studies showing that GD does not affect TC prognosis and some studies suggesting that GD may be associated with a worse outcome only if cancer is $\geq$ 1 cm.
Conclusion
In conclusion, a careful evaluation for patients with GD is essential, in order to check the development of possible incidental TC, even if they are nodule free, and total thyroidectomy should be the treatment of choice for Graves' disease in the presence of nodules.

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EP1038

Intrathyroidal Parathyroid Cysts

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Objective
Our aim is to describe the epidemiological, clinical and paraclinical features of intrathyroidal parathyroid cysts (PCs).
Materiel and Methods
We report 2 cases of intrathyroidal PC treated in our ENT department.
Results
We report 2 cases of non-functioning intrathyroidal PCs: 2 women (22 and 45 years old). They were referred to our department for anterior neck mass lasting for an average of 13 months. They had no compressive symptoms. Physical exam showed a soft, non-tender and well-limited anterior neck mass moving on swallowing. The mean size of the swellings was 3,5 cm. Ultrasonography of the neck revealed a right cystic thyroid nodule in the 2 cases. The mean size of the nodules was 42 mm. The serum TSH level was normal in all cases. The patients underwent right lobo-isthmectomy. Intra-operative examination suggested a benign cystic thyroid nodule. Post-operative histological exam confirmed the diagnosis of intrathyroidal PC. After an average follow-up of 3 years, no recurrence was noted.
Conclusion
Parathyroid cyst is a very rare entity. Ectopic sites are more uncommon. Intrathyroidal location is an exceptional ectopic location. To the best of our knowledge, eight intrathyroidal PC cases have been reported in the literature. They are often incidentally discovered in the histological exam after surgery.

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EP1039

Oculomotor paralysis and diabetes: what is the link?

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Introduction
Oculomotor palsies in diabetes are focal mononeuropathies. It is a diabetic neurological complication, relatively rare. The oculomotor nerves affected are mainly the external oculomotor nerve (VI), the common oculomotor nerve (III), and more rarely, the pathetic nerve (IV). We report the case of a type 2 diabetic patient in whom the diagnosis of oculomotor palsy was retained.
Observation
This is a 65-year-old diabetic patient, 4 years old, poorly followed under metformin and sulfonamide, was admitted for sudden onset ptosis associated with diplopia. Clinical examination: unilateral left ptosis, workup: hba1c at 7.5%; etiological workup: negative, ophthalmological examination and cerebral angiography: normal, therefore the diagnosis of common oculomotor palsy secondary to diabetic neuropathy was retained.
Discussion-Conclusion
Diabetes mellitus is the first cause of neuropathy in the world. Non-retinal diabetic complications including oculomotor damage represent 1 to 3% of the ocular manifestations of diabetes. It should be considered in any diabetic presenting with unexplained visual disorders. Its evolution is favorable in a few weeks, but recurrence on the same side or on the contralateral side is possible

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EP1040

Hashitoxicosis : a case report

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Introduction
Autoimmune thyroid diseases are frequent and very polymorphic pathologies. The same person can successively present with different manifestations. Graves' disease and Hashimoto's thyroiditis seem to be able to coexist. The name "Hashitoxicosis" has been suggested in this case, characterized by the sequential association, whatever the order, of hyper- and hypothyroidism. We report in this work, the case of a patient treated for autoimmune hypothyroidism and who subsequently presented with Graves' disease.
Observation
Aged 38, our patient presented at the age of 33 with autoimmune hypothyroidism and she was put on Levothyroxine for a period of 4 years. Considering her falling TSH levels at each quarterly check-up, we had to stop the replacement opotherapy, a few months later, another TSH level came back down to 0.001 µui/ml with an FT4 of 22 pmol/ml, and an FT3 at 8 pmol/l, with an autoimmunity assessment in favour of Graves' disease with a TSI level $>$ 40 ui/l and TPO antibodies $>$453 ui/l. The thyroid ultrasound revealed a thyroid of normal volume with heterogeneous echogenicity, without Doppler hyperaemia, completed by a thyroid scintigraphy that returned in favour of diffuse toxic goiter, suggesting Graves' disease. The patient was put on Antithyroid drugs.
Conclusion
The close relationship of these two forms of autoimmune thyroid disease explains the possible transition from one to the other, with successive phases of hyper-, eu- and hypothyroidism, linked to alterations of the balance between the various classes of antibodies.

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EP1041

A 3rd degree atrioventricular block revealing hypothyroidism: a case report

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Introduction
Hypothyroidism is a rare cause of atrioventricular block. We report the case of an 85 year old patient admitted with a 3rd degree AVB and in whom the biological work-up had objectified a hypothyroidism.

Observation
85-year-old patient, followed for thyreopathy for 20 years on LT4: 100 ug/d, Diabetic for 2 years on premixed regimen: 08-00-12 ui ;HTA for 5 years on amlodipine 5 mg/d presented to the emergency room for syncope. No signs of hypothyroidism, on clinical examination:Patient infiltrated;Hypertensive; bradycardic; polypneic; bilateral IMO, soft white, taking the cup reaching mid-leg; normal thyroid, on workup:CBC: hyperleukocytosis;TSH 9.22 ECG : Complete BAV Management was based on: increasing the dose of LT4 by 6.25 ug/d after cardiovascular evaluation; For diabetes: the patient was put on Lantus:10 ui 22h and rapid insulin according to capillary blood glucose
Discussion
The pathophysiology of atrioventricular block in hypothyroidism is not clear on the molecular level, the different clinical manifestations observed in hypothyroidism-associated cardiopathy can be explained by the genomic and non-genomic effects of thyroid hormones on cardiomyocytes
Conclusion
Evaluation of thyroid status is mandatory before any cardiac rhythm or conduction disorder

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EP1042

Navigating the differential diagnosis of thyrotropinoma and resistance to thyroid hormones

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Introduction
Syndrome of inappropriate secretion of thyrotropin (SITSH) is a rare condition characterized by uninhibited serum TSH in the presence of high thyroid hormones, usually caused by TSH secreting adenoma or resistance to thyroid hormones (RTH). Differential diagnosis between the two is often challenging due to their overlapping features.
Case report
We present the case of a 50-year-old postmenopausal woman with a history of -myocardial infarction in 2013, with angioplasty and 4 stent coronary placement. The patient was referred to our clinic for the evaluation of abnormal thyroid function tests (TSH = 3.25 µIU/ml RR = 0.3-3.6, FT4 = 30.2 pmol/l RR 9-24, FT3 = 11.8 pmol/l RR 3.1-6.8). The patient had no family history of thyroid disorders and a personal history showing a consistent pattern of a normal or elevated TSH level accompanied by elevated levels of thyroid hormones, which persisted despite the treatment with thiamazole 10 mg per day between 2017-2020. Clinically, the patient was euthyroid except for tachycardia, which was managed with metoprolol 300 mg per day. Our laboratory results confirmed inappropriate secretion of TSH (TSH = 4.07 µIU/ml RR = 0.3-3.6, FT4 = 1.73 ng/dl RR 0.7-1.48, TT4 = 15.37 µg/dl RR 4.8-11.7, TT3 = 244 ng/dl RR 76.3-220.8), normal pituitary function tests, negative anti-thyroid autoantibodies and thyroid ultrasound showed an unremarkable multinodular goiter. Due to anxiety the patient refused pituitary MRI, therefore screening CT scan was performed as an alternative diagnostic tool. It revealed an enlarged sella turcica (25/14/19mm) and a 18/11 mm pituitary tumor. Given the ischemic heart disease T3 suppression test was considered to be contraindicated. Furthermore, TRH is not available in our country. Alpha glycoprotein subunit levels were elevated (α-GSU = 1.89IU/l RR for postmenopausal women < 1.3). We decided to escalate the thiamazole dose to 20 mg per day and to reassess the patient in 4 weeks adding SHBG, a short-term somatostatin analog test, genetic screening for RTH and psychological counseling in order to obtain a MRI contrast enhanced pituitary scan.
Conclusions
The diagnosis of SITSH can be difficult to establish due to the low prevalence, insufficient awareness or experience of diagnosis or treatment, and unavailability of highly accurate diagnostic tests. This case was challenging due to the patient's ischemic heart condition, lack of access to certain diagnostic tools and the patient's refusal to undergo MRI examination. It is also important to remember that TSH-omas are very rare tumors, while pituitary incidentalomas are common. Therefore, a high level of suspicion and a thorough differential diagnosis algorithm are imperative.

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EP1043

The current state of the problem of thyroid pathology in iodine-deficient regions of the Russia

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Introduction
Interaction between genetic and environmental factors is the foundation of the pathogenesis of autoimmune thyroiditis (AIT). One of the important factors is iodine supply. Iodine deficiency is the main cause of goiter, dysfunction of the thyroid gland, disorders of mental and physical development. Main solution of that problem is the iodine salt consumption. It can decrease iodine deficiency, but the RF doesn't have general programs of salt iodization and has a lot of regions with low iodine supply.
Materials and Methods
The study was conducted in 3 districts of the Tula region (TR) ($n = 286$), 4 districts of the Chechen Republic (CR) ($n = 302$). The volume of the study was 588 adult people (over 18 years old). Examinations by an endocrinologist with taking anamnesis of life, evaluating anthropometric parameters, palpation of the thyroid gland. Participants of the study had thyroid ultrasound, analysis of venous blood for TSH, free fractions of T4, T3, antibodies to thyroid peroxidase (AT-TPO). The study is supported by the Russian Science Foundation, Grant No.22-15-00135.
Results
According to the results of the study, the prevalence of thyroid pathology is 81.79% in the CR, 42.66% in the TR. 19.9% participants in the TR, 27.15% in the CR have an elevated titer of AT-TPO in the blood serum. 19.9% participants in the TR, 21.2% in the CR have ultrasound signs of autoimmune thyroid changes. Prevalence of hypothyroidism due to AIT is 16.4% in the structure of the general thyroid pathology in the TR; there are 13.36% in the CR. 21% participants with hypothyroidism in the TR, 15% in the CR have the gland hypertrophy. The frequency of nodular goiter according to thyroid ultrasound is 95% in the general thyroid diseases in the TR, 83% in the CR, the combination of nodular goiter and AIT is 0.35% in the TR, 7.3% in the CR.
Conclusion
The TR and the CR are confirmed iodine-deficient regions. The obtained data on the prevalence of thyroid pathology and nodular goiter is higher than the data of official statistics (21.3% and 42% in the TR; 27% and 73.8% in the CR, FSSS, 2021). The obtained data reflect the problem of the high prevalence of thyroid pathology, including iodine deficiency thyroid diseases, in the whole area of the RF, in the absence of mass iodine prophylaxis at the state level. The data formed the basis for the creation of regional programs for the prevention of iodine deficiency.

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EP1044

Wernicke's encephalopathy complicating hyperemesis gravidarum associated with hashitoxicosis: Rare association

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Introduction
Wernicke's encephalopathy is a rare neurological disorder initially described in alcohol-dependent and malnourished patients. It is characterised by confusion, ataxia and nystagmus. It is caused by thiamine deficiency. We report the case of a patient with hyperemesis gravidarum and hashitoxicosis complicated by Wernicke's encephalopathy
Observation
A 22 year old patient, 1G0P, without any particular pathological history, was admitted to the intensive care unit with incoercible vomiting that had been evolving for one and a half months during a pregnancy estimated at 12 weeks' gestation, complicated by hydroelectrolytic disorders, in particular hypokalemia at 1.9 mmol/l and hyponatremia at 124 mmol/l. The clinical examination revealed confusion and dysarthria, the patient presented tachycardia at 128 bpm, normal blood pressure at 120/74 mmhg, no exophthalmos, her thyroid was palpable and not enlarged. The initial work-up showed liver cytolysis with ASAT and ALAT levels 4 times normal. Peripheral hyperthyroidism with TSHus < 0.005 µui/ml, T4l: 68 pmol/l. Cervical ultrasound showed a normal sized, homogeneous,

normo-vascularized thyroid. Anti-TPO antibodies were positive, while anti-R-TSH antibodies were negative. Brain MRI confirmed the diagnosis of Wernicke's encephalopathy. Treatment consisted of immediate thiamine administration, correction of fluid and electrolyte disorders, anti-emetic medication, and plasmapheresis for her hyperthyroidism. The clinical evolution was favourable with a normalisation of the ionogram and thyroid function tests.
Discussion
Wernicke's encephalopathy is an acute condition caused by severe deficiency of thiamine, which is an essential cofactor in many biochemical pathways in the brain. The overall incidence rate of Wernicke's encephalopathy is 0.04-0.13%. Hyperemesis gravidarum is an uncommon cause of Wernicke's encephalopathy. Hyperthyroidism is a hypermetabolic state in which thiamine utilisation is increased. This condition may precipitate Wernicke's encephalopathy in patients with reduced thiamine stores. Wernicke's encephalopathy due to hyperemesis gravidarum and hyperthyroidism is rare and difficult to diagnose. Its gold standard treatment is urgent thiamine substitution, allowing resolution of symptoms within hours to days depending on the severity of the disease.
Conclusion
Wernicke's encephalopathy is a potentially reversible disease if diagnosed and treated in time. Hyperthyroidism in patients with hyperemesis gravidarum may precipitate the onset of Wernicke's encephalopathy.

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EP1045

Myxoedema Coma, Life Threatening with Multiple Exacerbating Factors, Presenting with Bradycardia and Hypoglycaemia, Rare Interesting Experience with Bizarre Hormonal Imbalances

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A 91-year-old lady presented with bradycardia 'HR ~36, she was alert and conscious initially. Soon after the initial assessment, she was found unresponsive; with blood glucose of 0.8 mmol/l; bradyapnoec; BP 151/59; GCS 5/15; temp '32.8℃'. She was aroused after resuscitation with intravenous Dextrose, GCS 15/15 with an element of confusion, the temperature did not exceed 34.9℃ despite active warming. The patient looked in a low mood, barely audible, with bilateral reactive constricted pupils and hyporeflexia. The face was velvety and dry. She has hypothyroidism, AF on amiodarone, osteoporosis and multiple joint replacements. ECG showed atrial fibrillation with a slow ventricular response, low amplitude waves and QTc (469ms).
Initial investigation
Normal T4 and elevated TSH. INR 1.4 (on warfarin). Elevated creatinine. K+6.3; Na+ 123 mmol/l. Diagnosis of myxoedema coma was based on refractory hypothermia, AF with slow ventricular response, wide pulse pressure, hyporeflexia and hypoglycaemia with partial response to IV glucose. Liothyronine (T3) 80 mg-IV administered one hour after hydrocortisone 200 mg IV. Six hours after T3 administration, the core temperature increased to 36.6℃, the heart rate went up to 80 before settling at 60 bpm, QTc shortened to a normal range (410ms) and the patient regained consciousness and was communicating clearly.
Discussion
Myxedema coma reported in patients with undiagnosed hypothyroidism (1) and patients on levothyroxine as in amiodarone-induced myxedema coma (2) In this case it was multifactorial with amiodarone being a chief trigger. Omeprazole could be a contributory factor (3). Amiodaron inhibit conversion of T4 to T3 (5). With short half-life of the T3 in comparison to T4 and the very long half-life of amiodarone, serum-free T3 levels expected to decline soon with a single dose of Liothyronine - even after stopping the amiodarone. Causes of hyponatremia other than severe hypothyroidism was considered (4). Hyponatraemia, hyperkalaemia and hypoglyceamia indicate possible hypo-adrenal state
Conclusion
The threshold to suspect myxoedema coma should be lower in patients with a background of hypothyroidism; on amiodarone or with the following (bradycardia/bradypnea/hypothermia/hypoglycaemia) Heart rate, core body temperature, level of consciousness and respiratory rate are good parameters of response to thyroxine. When Amiodarone triggers myxoedema coma, continued T3 therapy with low doses may give better results than T4 therapy as the amiodarone effect on T4 conversion continues for a long time after discontinuation of therapy. Many factors should be considered to determine the correct dose of IV Liothyronine including age, weight, cardiovascular risk factors and metabolic demands.

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EP1046

A fatal case of myxedema coma

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Introduction and Backgrounds
Myxedema coma is a severe life threatening form of decompensated hypothyroidism which is associated with a high mortality rate. Infections and discontinuation of thyroid supplements are the major precipitating factors. It's characterized by a decreased mental status, hypothermia, bradycardia, hypotension, and hypoventilation. Very few cases of Myxedema coma have been reported till date, actual prevalence is unclear with the estimated incidence rate of 0.22 cases per million people per year. The purpose of the present article is to describe a fatal case of myxedema coma in an elderly woman occurring in the context of immunodeficiency.
Case Presentation
A 61-year-old woman with a past medical history of hypertension, type 2 diabetes, end-stage renal failure, miliary tuberculosis with pulmonary and peritoneal involvement under anti-bacillary treatment, autoimmune thyroiditis with discontinuation of L-thyroxine since 2 months. She was admitted to the emergency department for altered mental status. At admission her vital signs revealed a blood pressure of 20/70 mmHg, bradycardia at 54 bpm, hypothermia at 35 °C. The patient presented with dry depilated skin, vitiligo and generalized myxedema, the Glasgow Coma Scale was 10/15. The patient was transferred to the intensive care unit. The initial laboratory evaluation revealed the normochromic normocytic anemia and absence of electrolyte disturbances, Thyroid function was altered with thyroidstimulating hormone (TSH) of 100 mU/l and free thyroxin (T4) of 3.9 pmol/dl and free (T3) of 1.6 pmol/l. Diagnosis of myxedema coma was made and medical treatment was started. The patient was warmed gradually and oxygen was supplied via a mask. levothyroxin 300 µg was given via a nasogastric tube on third day after admission. The patient's clinical condition has not improved and she died 3 days later.
Discussion
Myxedema coma is an extreme manifestation in patients with untreated hypothyroidism. The diagnosis could be delayed because diagnostic laboratory data may not be available in a timely manner during emergency presentation. Our patient was also reported to have delayed diagnostic despite she was presented with all-common features of Myxedema coma, because she has other medical history as miliary tuberculosis and end-stage renal failure that make the first diagnostic suspected of a decreased mental status secondary to hyper uremia or central nervous system tuberculosis.
Conclusion
Myxedema coma is a lethal endocrine emergency. Thyroid hormone measurement allows the diagnosis. Protocols with rapid intravenous administration of high doses of thyroid hormones, together with warming and mechanical ventilation, may improve the prognosis.

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EP1047

Thyroidectomy in Graves' disease

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Introduction
Graves' disease is an immune system disorder that results in the overproduction of thyroid hormones. Treatment include: anti-thyroid medications, beta blockers, radioiodine therapy and surgery.
Objective
The aim of our study is to describe the role of surgery in the treatment of Graves' disease.
Patients and methods
We conducted a retrospective study including 40 patients who underwent surgery for Graves' disease in our department between 1996 and 2022.
Results
Our series included 30 women and 10 men, aged between 11 years and 63 years. All of the patients had hyperthyroidism. Thirty-eight patients had a goiter. A vascular thrill was perceived in 4 patients. Twelve patients had Graves' orbitopathy. All of the patients were treated with anti-thyroid drugs and β blockers. The average duration of medical treatment was 18 months. No patient was treated with radioiodine therapy. Indications for surgery were: failed medical therapy after 2 years of treatment (29 cases), a compressive goiter (4 cases), concomitant suspicious thyroid nodules (4 cases), side effects of antithyroid drugs (2 cases) and pregnancy (1 case). All of the patients had a total thyroidectomy. Seven patients developed postoperative complications such as transient hypocalcemia (6 cases) and recurrent laryngeal nerve palsy (1 case). No case of recurrent disease was noted.

Conclusion
Antithyroid drugs are used as initial treatment in Graves' disease. If remission is not achieved, radio-iodine therapy and surgery are considered as treatment options. Compared to surgery, radioiodine therapy can increase the risk of cancer and cause worsening of Graves' opthalmopathy, especially in children. Therefore, surgery may be a better option.

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EP1048

Hashimoto's thyroiditis associated with alopecia

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Introduction
Alopecia is an autoimmune disease (AID) affecting the hair follicles. Alopecia can become generalised and affect all hairy areas (universal alopecia). As with any AID, it may be associated with other AIDs. We report 2 cases of the association of alopecia with autoimmune thyroid disease (AITD).
Observation
The subjects were a man and a woman aged 48 and 54 years respectively. They presented with hypothyroidism. Hashimoto's thyroiditis (HT) was diagnosed and they were treated with L-thyroxine susbtituion therapy with favourable outcome. The thyroid disease was preceded since 24 years by an alopecia universalis, which appeared at the age of 23 years in the case of the man. In the other patient, this hypothyroidism was preceded by 2 other AIDs: alopecia universalis and vitiligo.
Discussion/Conclusion
Alopecia is a common condition with a significant psychosocial impact. It is a non-scarring alopecia, occurring most commonly in patches. The diagnosis is made clinically and does not require any further investigation in the absence of any particular symptoms. Alopecia can be associated with other AIDs, in particular thyroiditis, vitiligo and scleroderma. One study estimated the frequency of AITD in patients with alopecia to be 12.7%. Hypothyroidism was present in 92% of cases. It was found that alopecia in AITDs was most often severe, total or universal. Significantly higher levels of anti-thyroperoxidase antibodies and anti-thyroglobulins antibodies were found in the severe forms of alopecia.

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EP1049

Myopathy in hyperthyroidism : a retrospective analysis of 6 cases

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Background and aim:
Hyperthyroidism status can be complicated by polymorphic neuromuscular manifestations sometimes revealing. In the majority of cases, these disorders regress during the transition to euthyroidism. We report in this work 6 observations illustrating the neuromuscular manifestations seen in hyperthyroidism.
Observations
We report two cases of chronic myopathy: a man and a woman aged 47 and 55 years respectively, hospitalized for hyperthyroidism associated to generalized amyotrophy with functional impotence. The EMG confirmed the muscular damage. Thyrotoxic periodic paralysis was noted in 2 patients, a man and a woman, aged 27 and 34 years respectively. They presented with spontaneously resolving paralytic attacks predominantly in the lower limbs lasting 3 to 24 hours and associated with thyrotoxicosis and hypokalemia. The fifth and sixth patients had peripheral polyneuropathy associated with thyrotoxicosis. They were a 39-year-old woman and a 45-year-old man. The woman presented with parasthesia of the extremities and gait disorders. The man presented with flaccid paraparesis. The electrophysiological study showed neurogenic damage in both cases. Graves' disease was the cause of hyperthyroidism in 5 cases. Hashimoto's disease was incriminated in the remaining case.
Discussion
In all of these cases, early treatment led to a dramatic improvement in neuromuscular symptoms. The pathophysiological mechanisms of these disorders remain difficult to elucidate and require more advanced studies on larger cohorts of patients

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EP1050

Nodular Dystrophy Revealing an Ectopic Thyroid : About A Case

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Introduction
Thyroid ectopia is a rare pathology linked to a migration defect of the thyroid gland during its embryonic development. It is most often asymptomatic, but can be revealed by dysthyroidism, or a cervical or thoracic mass. We report the case of an ectopic thyroid revealed by a mediastinal mass.
Observation
61-year-old patient, with no particular history, followed for a plunging multi-hetero-nodular goiter which cervical ultrasound showed an enlarged thyroid, whose largest nodule was on right lobe measuring 12 x 18 x 29 mm classified EUTIRADS 3, and the most pejorative on left lobe measuring 11 x 16 x 22 mm classified EUTIRADS 5. Cervicomediastinal CT showed an anterior mediastinal mass with CT characteristics similar to those of the thyroid parenchyma. The patient underwent a total thyroidectomy with resection of the mediastinal mass. The anatomo-pathological examination noticed a multinodular thyroid dystrophy, and on the mediastinal mass a dystrophic thyroid nodule, without signs of malignancy.
Conclusion
Pathological changes that affect normal ectopic thyroid can occur in ectopic tissue. Hence the importance of long-term clinical and biological monitoring and possible fine needle biopsy of ectopic thyroid tissue.

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EP1051

Neutropenia secondary to synthetic antithyroid drugs: about 5 cases including one case of agranulocytosis

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Introduction
Hematological toxicity is the main risk of synthetic antithyroid drugs (ATS); the major form is acute agranulocytosis requiring adequate and urgent management. The literature concerning neutropenia and agranulocytosis under ATS is relatively poor, based on rare studies, with often small numbers of patients, and most often concerning American or Japanese populations treated.
Purpose of the study:
Report our experience in the endocrinology and metabolic diseases department of the CHU IBN ROCHD in Casablanca, through 5 cases of neutropenia secondary to ATS.
Method
Descriptive retrospective study including patients followed in the endocrinology department of the CHU Ibn Rochd in Casablanca, for hyperthyroidism who presented with neutropenia secondary to ATS during the period 2021–2022.
Results
All our cases were female with an average age of 43 years (24-63 years), two patients (40%) had multi hetero nodular goiter and three patients (60%) were followed for Graves' disease. Concerning the ATS, all the patients were under carbimazole with an average dose of 22 mg/day (10-30). Only one patient presented with a fever of 39.6°C and erythematous throat with agranulocytosis, while the other four patients had no signs of infection with neutropenia ranging from 580 to 1300/mm3 discovered as part of the monitoring report. Discontinuation of ATS was recommended in all cases with oral corticosteroid therapy (prednisolone at an average dose of 40 mg/d) with three patients who were initially on a bolus of solumedrol. The use of a broad-spectrum antibiotic therapy was envisaged in two patients and that of hematopoietic growth factors in a single patient. The evolution was favorable in four cases with neutropenia (80%) with normalization of PNN and regression of signs of hyperthyroidism, while the patient with agranulocytosis had died in intensive care.
Conclusion
The seriousness of the severe neutropenia and especially of the agranulocytosis which can be observed under ATS, justifies good patient education as well as close monitoring of the blood count, in particular during the first two months of treatment.

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EP1052

Two rare cases of Riedel's thyroiditis

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Introduction
Riedel's thyroiditis (RT) is a rare chronic inflammatory disease characterized by a dense fibrosis that replaces normal thyroid parenchyma. The most common manifestation is a stony hard thyroid mass, commonly associated with compressive symptoms. Histological confirmation is essential for diagnosis and the main differential diagnosis is the anaplastic thyroid cancer. The management is challenging and there is no agreed standard treatment, since only a few cases have been described.
Clinical Case
Case 1: A 46-year-old woman presented with a 2-month history of painless anterior neck mass and dysphonia. Neck examination revealed a hard and painful thyroid mass. Blood tests showed subclinical hyperthyroidism and positive thyroglobulin antibodies (TgAbs). Ultrasound showed a 39 mm solid, hypoechoic and heterogeneous nodule with poorly defined margins. There was no cervical lymphadenopathy. Tc99m *scintigraphy* revealed a cold nodule. Fine-needle aspiration biopsy (FNAB) was non-diagnostic. The patient underwent total thyroidectomy, requiring postoperative emergency tracheostomy. Laryngoscopy revealed bilateral vocal cord paralysis. The histological study was compatible with RT. The tracheostomy was closed 8 weeks after surgery. Prednisolone 40 mg and, posteriorly, tamoxifen 20 mg were started with symptomatic relief. Both medications were tapered off. Currently, 7 years after diagnosis, the patient is asymptomatic.
Case 2 A 67-year-old woman with thyroid nodular disease was proposed for right hemithyroidectomy. Intraoperatively, a hard mass adhering to the trachea and right carotid artery was found, making resection impossible. Therefore, a intraoperative biopsy was performed to establish histological diagnosis. Histopathology was consistent with RT and the patient was referred to Endocrinology consultation. She had no compressive symptoms and physical examination revealed a 5 cm stony hard thyroid mass. There was no cervical lymphadenopathy. Blood tests showed hypothyroidism and positive TgAbs. Ultrasound showed a 52 mm solid, hypoechogenic and heterogeneous mass in the right thyroid lobe. A FNAB was performed with a non-diagnostic result. A neck CT confirmed a voluminous solid mass in the right lobe without cleavage planes with cervical vessels and trachea. Given the clinical stability and absence of symptoms, it was decided to maintain active surveillance. After 5 years of follow-up, the patient remains asymptomatic and the thyroid mass is stable on ultrasound.
Conclusion
Although malignancy is more frequent, in patients presenting with a hard thyroid mass RT should be considered as differential diagnosis. Our cases highlight the challenges inthe diagnosis and management of this rare disease and the importance of taking an individualized approach.

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EP1053

Tuberculosis of the thyroid gland: a case study

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Introduction
Thyroid tuberculosis is a rare entity even in countries like Algeria where tuberculosis is endemic.
Observation
We report the case of a 40-year-old woman, with a history of hypertension and severe renal failure, consulting for recent cervical swelling evolving in a context of asthenia, nocturnal fever and weight loss. The clinical examination found a compressive goitre. The biological assessment objectified a primary hypothyroidism and an inflammatory syndrome. Cervical ultrasound revealed a poorly circumscribed strongly hypoechoic area in the left thyroid lobe associated with multiple left cervical adenopathies. The diagnosis of thyroid lymphoma was evoked, the patient benefited from several inconclusive fine needle punctures. Biopsies of the thyroid gland and adenopathies were performed; the histological examination objectified epithelioid granulomas with caseous necrosis.
Discussion
Tuberculosis of the thyroid gland accounts for 0.1-0.4% of all localizations. It mainly affects young adults with a preponderance of the female sex. The clinical picture is not specific. It is most often a basicervical tumefaction of progressive installation accompanied by satellite adenopathies and general signs suggesting cancer in first intention. Thyrotoxicosis or hypothyroidism may exceptionally be observed. The appearance on cervical ultrasound is not specific. Most often, cytopuncture is not contributory. Histological examination confirms the diagnosis. The treatment of thyroid tuberculosis is medico-surgical. Our patient was put on anti-tuberculosis treatment and she was designated for surgical management.

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EP1054

Jougerot sjogreen syndrom revealing autoimmun hypothyroidism

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Introduction
Jougerot –sjogreen syndrom is an auto-immune exocrinopathy secondary to the interaction between a favorable ground and environmental factors that can lead to the disease. Thyroiditis can precede sjogreen's syndrom or follow it, just as the two diagnoses can be made at the same time.
Case report
46-year-old female patient, type 2 diabetic on oral antidiabetic 2g/d, followed for sjogreen jougerot syndrom retained in the face of occulo-buccal dry syndrom, cervicothoracic pain, schirmer test positive salivary gland biopsy under corticosteroid therapy. On questionning, the patient reported inflammatory polyarthralgia associated with chronic constipation and asthenia. Objective physical examination morbid obesity with BMI = 44 kg/cm^2, palpable thyroid increased in size. On the balance sheets TSH = 6.7uui/l, T4 = 11pmol/l on the cervical ultrasound : homogenous thyroid, with regular contours, normo vascularized on the doppler seat at the left mid-lobe level hypoechogen formations formations measuring 12.6*7.3mm classified Eu-tirads 3, at the left lower lobe level hypoechogen formations measuring 9*7mm Eu-tirads 2with positive anti-TPO antibodies. The patient was put on levothyrox 75ug/d.
Discussion
Jougerot-sjogreen syndrom is a dysregulation of the immune system by B cell hyperactivation. It is probably the systemic autoimmun disease most frequently associated with autoimmun thyroiditis with an estimated prevalence of 20%. The strong association between the presence of thyroid antibodies for patients with autoimmun hypothyroidism with jougerot syndrom. The association does not seem to result from a disease caused by the other, but results from the appearance of entities to which a context genetically predisposes the subjects, such as patients with HLA DRW3 and HLAB8 haplotypes.
Conclusion
The jougerot sjogreen syndrom and auto-immun thyroiditis their association reflects the presence of a common genetic ground on which are added environmental factors which are added environmental factors which determine the clinical aspects. Regular assessment of thyroid function is necessary in any patient with jougerot sjogreen syndrom.

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EP1055

Transient hypothyroidism post radioiodine therapy

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Introduction
Grave's disease is an autoimmune disorder and is considered the most common cause of hyperthyroidism. Its treatment options include medical therapy, radioactive iodine (RAI), and surgery. RAI is commonly employed for Grave's disease regarding its efficiency and safety. Definitive hypothyroidism is the main goal of RAI and is typically achieved within the first 3 to 6 months of therapy. Transient hypothyroidism and recurrence of hyperthyroidism after RAI might occur in some patients. We herein describe 2 cases of transient hypothyroidism following RAI.
Observations
Case 1 is a 67-year-old patient with a history of hyperthyroidism revealed by cardiothyreosis (atrial fibrillation and heart failure) 20 years ago with levels of TSH < 0.05 mUI/l. TSH receptor antibodies were positive confirming the

diagnosis of Grave's disease. He received RAI after 2 months of methimazole. Six months later he developed hypothyroidism requiring thyroxine supplementation. During the follow up, he presented low TSH levels although dose tapering, leading to the discontinuation of thyroxine after 8 years of supplementation. He remained euthyroid for 7 months then redeveloped hypothyroidism. Case 2 is a 52-year-old patient with type 1 diabetes mellitus. Grave's disease was revealed by weight loss and a goiter. His initial TSH was suppressed He was treated by RAI he was hypothyroid post RAI and was put on thyroxin supplementation until he started in a 3 year time presenting with persistently low TSH levels despite lessening the doses, we decided not to follow through with treatment and the patient remained euthyroid despite a 4 year period of treatment withhold

Discussion

Transient hypothyroidism post RAI should be thought of after radioiodine therapy when patients present with a lessened daily needs of thyroxin. It leads to a variably lasting period of euthyroidism necessitating further monitoring of TSH levels.

Conclusion

Grave's disease incidence is growing worldwide. RAI being the most common treatment for either complicated or recurrent cases or within patient's preference. Transient hypothyroidism post radioiodine should be taken into account and further studies are needed to confirm it, describe what might be its causes and predicting factors.

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EP1056

Association of Crohn's disease and Hashimoto's thyroiditis : a case report

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Introduction

Crohn's disease is a chronic inflammatory bowel disease, most commonly affecting the terminal ileum and colon. In the other hand, Hashimoto's thyroiditis is a chronic autoimmune inflammation of the thyroid gland. The association between the 2 diseases is rare. We report the observation of a patient with this association.

Observation

A 23-year-old female patient who consulted for persistent diarrhea, rectorrhagia, abdominal pain, bradycardia and asthenia. A workup was ordered in favor of hashimoto's autoimmune hypothyroidism with TSH at 12 (normal value: 0.4-3.78 IU/ml), free T4 at 0.4 (normal value: 0.7-1.48 ng/dl), anti-thyroperoxidase antibody at 200 IU/ml (normal value: $<$0.1 IU/ml). The cervical ultrasound was in favor of thyroiditis. The patient was put on Lthyroxine supplementation; concomitantly, the patient benefited from a colonoscopy and biopsy which anatomopathological examination was in favor of the diagnosis of Crohn's disease.

Discussion and conclusion

The coexistence of Crohn's disease and Hashimoto's thyroiditis is rare. This relationship has been explained by the coexistence of genetic and immunological factors. Several studies have shown that the immune response is polyclonal in both diseases. At present, there is no clear explanation for the coexistence of autoimmune thyroid disease and Crohn's disease, a random coexistence remains possible but the increasing accumulation of reported cases requires further analysis to clarify the etiology of these associations.

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EP1057

Diagnostic performance of fine needle aspiration biopsy in the diagnosis of medullary thyroid carcinoma

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Medullary thyroid cancer (MTC)is a very polymorphic tumour, it remains difficult to diagnose, especially in cytology. The MTC is characterized by a polymotphic cell population, the amyloid stroma is found in 43 to 81% of cases. In this retro and prospective study carried out over 5 years, we included 45 lesions (8 nodules, 35 lymph nodes and 2 cervical masses) these lesions were punctured and the cytological results were compared with the definitive histology. On cytology, 13 lesions (29%) were benign, 14 lesions (31%) were malignant and 18 lesions (40%) were MTCs. After surgery, the definitive histology confirms the MTC in 32 lesions (5 nodules, 25 lymph nodes and 2 cervical masses). For the remaining 13 lesions, 9 were true negatives and 4 were follicular carcinomas of the thyroid. Finally, fine needle aspiration biopsy has a sensitivity of 53.12% and a specificity of 92.3% for the diagnosis of MTC. It is a good diagnostic tool for follicular carcinoma but less so for the diagnosis of MTC.

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EP1058

Lymph node metastasis in medullary carcinoma of the thyroid gland

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Introduction

Medullary thyroid carcinoma (MTC) is a neuroendocrine malignancy of the thyroid C cells. Metastatic spread commonly occurs to cervical lymph nodes.

Methods

This is a retrospective study including 8 cases of medullary carcinoma of the thyroid gland between 2000 and 2020.

Results

The sex-ratio (M/F) was 0.125. The mean age of our patients was 55.87 years. No personal or family history of multiple endocrine neoplasm was found. Symptoms included: a cervical mass in all cases, dyspnea in 2 cases and a flush syndrome in 2 cases. On physical exam, a level 2 lymph node was palpated in 3 cases. On ultrasound, thyroid nodules were classified as EU-TIRADS 4 or 5 nodules with lymph node showing malignant features in 4 cases. Fine-needle aspiration was performed in 3 cases and did not suggest the diagnosis of a MTC. Surgery included: total thyroidectomy with central lymph node dissection in 1 case, central and lateral lymph node dissection in 7 cases. It was bilateral in 3 cases. Extemporaneous exam suggested MCT in one case. All patients had lymph node metastases. The tumor mean size was 57mm, multifocal in 1 case, with extra-thyroidal extension in 1 case. There was no evidence of distant metastasis on CT-scan in all cases. There was also no evidence of hyperpathyroidism or pheochromocytoma. Six patients had radiotherapy. There was 1 case of lymph node recurrence and 2 cases of distant recurrences (lung and bone metastases).

Conclusion

In MTC, Surgery is the best treatment option. Patients with MTC should receive lateral lymph node dissection especially when calcitonin levels are elevated, even in the absence of lymph node metastasis on clinical exam and imaging.

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EP1059

An unexpected discovery of MEN 2B Syndrome in an adolescent - a case report

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Introduction

Multiple Endocrine Neoplasia Syndrome 2B (MEN 2B) is a very rare genetic disorder which affects the thyroid and the adrenal glands, the development of mucosal neuromas and the general appearance of the patient's body. Therefore, we can encounter Medullary Thyroid Carcinomas (MTC), adrenal sympathetic paragangliomas (or Pheochromocytomas) and habitus Marfanoid. The disease represents a challenge for every clinician, especially if it occurs in a child.

Methods

Clinical exam, Blood work, CT scan, genetic testing, pathology exam.

Case report

We present the case of a 12-year-old girl who came in the Pediatric Endocrinology Department with a right thyroid solid mass, for which she was admitted. Upon clinical examination, the patient was thin and tall, with flexible joints, suggesting Marfanoid habitus and also mucosal neuromas were found in the oral cavity, with normal blood pressure, no palpitations, no sweating. No significant family history was discovered. Thus, MEN 2B syndrome was a possible diagnosis. The general blood work and thyroid function were normal, calcitonin was 1100 times over the upper normal limit, while serum PTH and urinary metanephrines and normetanephrines in the 24 h sample urine were within normal range. We also performed a thyroid ultrasonography which revealed 2 hypoechoic nodules in each thyroid lobe, with macrocalcifications. We

performed a CT scan which showed the 2 nodules, with no lymphatic nodes suggesting metastases. The patient underwent a total thyroidectomy with bilateral cervical lymph node dissection. The pathology report came back positive for MTC in both nodules, with no extension to the lymph nodes, confirming our diagnosis of MEN 2B. The next step was genetic testing from the patient's blood to identify if she had the germinal mutation of the RET gene, which came back positive for the p.Met918Thr in exon 16. Obviously, we had to test the patient's parents and brother and there were all negative for the mutation.
Discussions
The patient was brought to us because of a thyroid nodule which turned out to be a MEN 2B syndrome with bilateral MTC, mucosal neuromas and Marfanoid habitus, without the implication of the adrenal glands, with a de novo mutation of the RET gene. The fact that it was discovered in a child makes it even more rare.
Conclusions
MEN 2B Syndrome is a very rare genetic disorder in the general population, making it even more unexpected to be found in the case of a child.

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EP1060

Test for determination of stimulated calcitonin level

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Assessment of basal calcitonin as the main marker of medullary thyroid cancer (MTC) was introduced into routine practice in the Republic of Belarus more than 10 years ago. A number of laboratory and clinical factors can influence the result of this parameter determination. Equally important is the gender, age, weight, the deviation of the serum calcium level, certain medications.
The aim
Of the study was to develop and implement of stimulated calcitonin test to solve the problem of low specificity of basal calcitonin test for MTC diagnosis.
Materials and methods
The test protocol includes 1) determination of basal calcitonin level in the serum - blood sampling before the administration of calcium gluconate; 2) determination of the stimulated calcitonin level in the serum - blood sampling in 2 and 5 minutes after intravenous administration of a 10% solution of calcium gluconate. Tubes with blood must be immediately placed on ice, as calcitonin decomposes at room temperature. It is recommended the estimated dose of a 10% solution of calcium gluconate is indicated in terms of elemental calcium and is 2.0-2.5 mg/kg. The maximum allowable dose (all patients weighing more than 70 kg) is 20 ml of a 10% calcium gluconate solution. The drug is administered intravenously slowly over at least 30 seconds. In this case, the patient must be in a horizontal position.
Results and discussion
In the Republic of Belarus stimulated calcitonin test was carried out in 2017 in the consultative and diagnostic department of thyroid pathology of the Republican Center for Thyroid Tumors. Within the framework of the project, the test was carried out in 50 patients, preventive thyroidectomy was performed in 20, the systematization and analysis of the results continues. Possible adverse reactions during the test are a feeling of heat, a decrease in blood pressure, heart rhythm disturbances, fainting, cardiac arrest. Contraindications to the test are hypercalcemia and the simultaneous intake of cardiac glycosides.
Conclusions
Thus, the introduction and conduct of a calcitonin stimulated test showed its effectiveness for the differential diagnosis of nodular thyroid pathology (primary diagnosis of MTC in patients with nodal pathology of uncertain malignancy potential, taking into account the hereditary factor and with elevated levels of calcitonin); to verify the progression of the tumor process in patients with MTC (detection of early biochemical recurrence). This method can confirm a stable remission of the disease and allow women with MTC to plan pregnancy.

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EP1061

Prolonged Survival in Follicular Thyroid Cancer with Bone Metastasis

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Introduction
Follicular thyroid cancer (FTC) accounts for 12% of differentiated thyroid cancers (DTC). It is frequently complicated by bone metastasis (BM), which impact quality of life (QOL) and decreases the 10-year survival rate to 13-21%.
Case Report
A 53-year-old woman followed at the Pain Clinic for over 10 years for lower back pain, had been operated three years before due to lumbar disc herniation. Pain relapsed one year after surgery and was resistant to analgesics. On physical examination (2010) a right thyroid mass and lower-extremity hypoesthesia were noted. Spine CT scan documented a 60x98 mm lytic mass at left pelvis and sacrum. Core biopsy revealed FTC with positivity for thyroglobulin (Tg) and TTF1. Thyroid ultrasound showed a bulky right thyroid nodule and suspicious right laterocervical lymph nodes. Laboratory tests revealed normal thyroid function, Tg 30334 ng/ml and negative TgAtbs. Thoracic CT documented pulmonary micrometastasis. Total thyroidectomy with cervical lymphadenectomy was performed. Histopathology showed a 7 cm widely invasive FTC with extra-thyroidal extension and lymph node metastases. Six weeks post-surgery Tg was 74560 ng/ml (TSH 8.9 uUI/ml). Within five years, she received four radioactive iodine (RAI) treatments with post-RAI scans demonstrating 131-I avid metastasis. After the second RAI, Tg dropped to 513 ng/ml, but TgAtb became positive. A debulking surgery with sacrum stabilization was also performed. Lenvatinib (LVT) was started seven years after diagnosis, due to imaging and biochemical evidence of metastatic progression, despite suppressive levothyroxine therapy and cumulative 131-I 29.7 Gbq. The dosage was reduced from 24 to 20 mg/day due to diarrhea. Arterial hypertension and anorexia developed and were pharmacologically controlled. She had good clinical and biochemical response (Tg decreased and stabilized; TgAtbs decreased and became negative). Thoraco-abdominal CT and spine MRI showed no significant signs of progression. Lumbar pain was controlled with opioids. After 1.5 years since LVT, there was pulmonary metastasis progression, despite biochemical stability. After an additional two years since LVT, she had substantial biochemical progression (last Tg level 41059 ng/ml in OCT-2022) and persistent vertebral pain. Significant BM progression was documented on 18-F-FDG PET and CT scans, the latter also revealing pulmonary disease progression. Tumor RET status was negative. The initiation of cabozantinib is under consideration.
Discussion
We describe a case of FTC with BM at presentation, with prolonged survival, currently 13 years. Although mostly not curative, a multimodal therapeutic approach should be employed by experienced teams to improve patienťs QOL and survival.

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EP1062

Papillary carcinoma of the thyroid in Basedow disease : case report

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Introduction
The occurrence of Basedow disease does not eliminate the possibility of an associated thyroid cancer. Thyroid carcinoma in Basedow disease is particularly rare (1 to 2%). Most often, it is a papillary carcinoma. This is most often a chance discovery. We report a case of a papillary carcinoma in a Basedow disease taken care of in our department.
Case Report
This was a 39-year-old hypertensive diabetic woman followed in endocrinology for Basedow' disease under medical treatment, referred to our department for management of an anterior basal cervical swelling rapidly increasing in size. anterior cervical swelling of 6 cm of MA associated with multiple supracentimetric left jugular carotid adenopathy as well as bilateral proptosis. The rest of the ENT examination was without abnormalities. Cervical ultrasound showed a multinodular thyroid goiter with an upper left nodule classified EUTIRADS V associated with bilateral lymphadenopathy, especially at the level of bilateral IIb and IIA chains with a 'thyroid-like' appearance. The patient had a total thyroidectomy associated with bilateral recurrent mediated dissection and left functional dissection. The frozen section examination found a carcinoma papillary lymphadenopathy and metastatic papillary carcinoma. Definitive anatomy pathology examination confirmed the diagnosis of multifocal and bilateral papillary carcinoma with a crossing of the capsule associated with lymph node metastasis at the level of the adenopathy of the recurrent and lateral mediastinal dissection. The patient was referred to IRAtherapy, she received 100 Mci of radioactive iodine with white cartography with good evolution without recurrence after one year of follow-up.

Conclusion
According to data from the literature, the incidence of thyroid cancer in Basdewo disease is rare (0.1 – 9.8%). The histological type is a papillary carcinoma in most cases.
• The subsequent management is similar to that of differentiated thyroid cancers, namely isotopic ablation at I131 and a braking treatment with L-thyroxine.

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EP1063

Parkinson's disease associated to Hashimoto's thyroiditis

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Introduction
Parkinson's disease (PD) is one of the most common neurodegenerative disorders characterized by bradykinesia, tremor, rigidity and postural instability as well as neurocognitive impairment and depression. Studies found a significant association between thyroid dysfunction and an increased risk of PD. We report the case of a patient treated for PD who had also Hashimoto's thyroiditis, and we discuss the association of thyroid dysfunction with risk of PD.
Case report
Female patient, aged 52 years. Followed for 2 and a half years for Parkinson's disease, clinically retained for bradykinesia, rigidity, tremor, treated with L-Dopa Benserazide and trihexyphenidyl hydrochloride. She presented weight loss, palpitations and intermittent diarrhea. The clinical examination noted a goiter and normal heart rate to 70 bpm. Thyroid function tests showed hyperthyroidism TSH us $<$ 0.01 uUl/ml, fT4: 51.9 pmol/I, fT3: 13.9 pmol/I. Anti-thyroid antibodies measurement indicated positive anti-tpo Ab to 663.5 IU/l and negative anti-TSH receptor Ab. Thyroid ultrasound examination revealed typical image of Hashimotós thyroiditis. The diagnosis of Hashitoxicosis was retained. In one month follow-up, fT4 level decreased to 34 pmol/l. Follow-up with biological monitoring is planned for the diagnosis and management of hypothyroidism stage.
Discussion
There is a correlation between thyroid function and PD, but the mechanism is not completely clear. Patients with thyroid dysfunction have an increased risk of developing PD. Oxidative stress is one of the chief contributing factors to dopaminergic neuron loss and PD progression. Both hyperthyroidism and hypothyroidism are related to oxidative stress and cellular damage. Patients with autoimmune diseases, such as Hashimoto's thyroiditis, Graves disease, amyotrophic lateral sclerosis, multiple sclerosis, and rheumatoid myalgia, had an additional 33% risk of PD. Besides the direct effects of thyroid hormone on dopaminergic neuron and skeletal muscle function and shared genetic risk, the association may be driven by autoimmunity; autoimmune response and neuroinflammation may play a role in the pathogenesis of PD. In addition, studies have suggested that presence of thyroid auto antibodies (anti-thyroid peroxidase and antithyroglobulin) are associated with neurodegenerative disorders such as multiple system atrophy and cerebellar degeneration. However, it's unknown whether and how thyroid autoantibodies affect the dopaminergic neurons and risk of PD.
Conclusion
Many studies have shown that there is a correlation between thyroid dysfunction and PD, but the mechanism is incompletely clear. Further investigations should be conducted to provide clear evidence and to identify the mechanism responsible for this association.

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EP1064

Case of Subacute Thyroiditis after receiving the SARS-CoV-2 vaccine and the Covid-19 infection 6 months later in the same patient

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A 43-year-old woman received the CoronaVac COVID-19 vaccine produced by Sinovac Biotech in September 2021. 1 month after the last dose of vaccine (10/2022), she developed pain in her right neck, palpitations, and fever. Laboratory studies revealed severe thyrotoxicosis (TSH - 0.1 mIU/ml, high FT4) and increased ESR - 59 mm/h; Ultrasound showed an asymmetric thyroid due to enlargement of the hypervascular right lobe. The left lobe was intact. She was diagnosed with subacute thyroiditis developed after CoronaVac vaccine and was treated with steroids for 3 months. She had an immediate improvement after the first dose of the methylprednisolone. After this episode, thyroid function tests were checked regularly and were normal. In January 2022 the patient tested positive for COVID-19. In April 2022, she developed pain in the left side of her neck, fever, and palpitations. The left lobe of the thyroid gland was painful on palpation, the right lobe was painless. Thyroid ultrasound revealed an increase in the left lobe compared to the previous report: $3.8 \rightarrow 8.5$ cm^3, thyroid was heterogeneous, with inflammatory infiltration areas. TSH done 2 weeks ago showed the presence of subclinical hypothyroidism (TSH - 5.8 mIU/ml). CBC showed anemia, an increase in ESR of 62 mm/h and elevation of CRP. TFT were re-evaluated: TSH - 0.11 mIU/l, FT4 and FT3 were high normal. Thyroid scintigraphy showed absence of uptake in both lobes - 0%. Based on performed investigations, the patient was diagnosed with subacute thyroiditis, this time after a covid infection. She was given NSAIDs and propranolol, but the pain in her neck worsened, it was extremely difficult for her to swallow even liquids, and any touch on her neck was very painful. The fever was persistent despite the use of NSAIDs. Due to the deterioration of the clinical picture, despite taking ibuprofen 1200 mg per day, methylprednisolone 32 mg was prescribed with appropriate gastroprotection and potassium supplementation. Again, immediately after the first dose of the steroid, the patient felt a marked improvement, she was prescribed methylprednisolone at a dose of 32 mg for 1 month, and then down titrated according to laboratory data and clinical picture, and discontinued in July 2022. Since then, her thyroid function tests have been normal and she feels well. Besides the thyrotoxic phase of subacute thyroiditis, laboratory testing revealed vitamin D deficiency, vitamin B12 deficiency, and iron deficiency. The patient was prescribed the supplements for the aforementioned deficiencies.

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EP1065

Diagnosis and management of a thyrotoxicosis storm on unknown hyperthyroidism

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Introduction
In the spectrum of endocrine emergencies, thyroid storm is one of the most critical complications. Recognition and appropriate management of life-threatening thyrotoxicosis is vital to prevent the high morbidity and mortality that may accompany this disorder. The incidence of thyroid storm has been noted to be less than 10% of patients hospitalized for thyrotoxicosis; however, the mortality rate secondary to thyroid storm ranges from 20 to 30%. We report in this work, the case of a patient with unknown Grave disease, who had a thyreotoxicosis storm after cholestectomy.
Observation
52-year-old patient, 20 days before his thyrotoxicosis storm, our patient presented with acute pancreatitis on vesicular lithiasis, which required the realization of a cholecystectomy, our patient did not show any clinical sign of thyrotoxicosis before surgery, but the occurrence of a hypertensive peak, tachycardia at 147 beats/min and significant dyspnea, a thyroid assessment was carried out, returning in favour of hyperthyroidism with a TSH level $<$ 0.01µui/ml and an FT4 level: 69 pmol/l, the electrocardiogram found an atrial fibrillation, the diagnosis of a thyroid storm was retained on clinical and biological criteria (scored at 50 according to the Wartofsky score) and the patient was transferred to an intensive care unit, where he received appropriate management. Subsequently, our patient received radical treatment for his hyperthyroidism.
Conclusion
Thyrotoxicosis and thyroid storm represent a critical diagnostic and therapeutic challenge to the clinician. Recognition of life-threatening thyrotoxicosis and prompt use of medications aimed at halting the thyrotoxic process at every level is essential to successful management. A set of therapeutic weapons exist: the treatment aimed at stopping synthesis of new hormone within the thyroid gland, halting the release of stored thyroid hormones from the thyroid gland, preventing conversion of T4 to T3, and providing systemic support of the patient. All of which can stop the thyroid storm and save the patient from critical complications. Once this transition occurs, definitive therapy of thyrotoxicosis can be planned.

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EP1066

Ectopic thymus discovered during thyroid surgery

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Introduction
The thymus is a primary lymphoid organ and the initial site for development of T cell immunological function. It originates high in the neck in early fetal life and reaches its definitive location in the mediastinum after a process of descent, generally leaving no trace behind. Occasionally, during this descent, remnants of thymic tissue can be implanted along the cervical pathway, later appearing as a cervical mass.
Case Report
This is a case of a 39-woman undergoing surgery for a left thyroid nodule. During surgery, a yellowish mass located behind the lower pole of the left thyroid lobe was discovered. The mass was not removed. A biopsy was performed. On histologic examination, it corresponded to a thymic tissue.
Conclusion
The third and fourth pouches are responsible for the development of the parathyroid glands, the thymus, and a portion of the thyroid gland. Ectopic parathyroid tissue can be found anywhere along their pathway of descent. However ectopic thymus is rarer and is usually found at the mediastinum. The diagnosis of ectopic thymus is difficult and can be misleading, it should be suspected in case of yellowish tissue located posteriorly to the thyroid gland. If ectopic thymus is suspected, frozen section biopsy should be performed. If the diagnosis is confirmed, the mass should not be excised unless it is causing dyspnea or dysphagia.

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EP1067

Hepatic Encephalopathy Complicating Graves 'disease: A Case Report

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Introduction
Hepatic encephalopathy is a neuropsychological syndrome complicating a chronic liver disease (cirrhosis), rarely acute (fulminant hepatitis). We report the case of a patient with Graves' disease who suddenly presented with hepatic encephalopathy.
Case Report
S.B., a 48-year-old woman followed for Graves' disease treated with antithyroid drugs and also presenting vitiligo, was admitted to our facility for a relapse of Graves' disease with major hyperthyroidism (TSH < 0.05 and T4l: 100 pmol) and cholestatic jaundice. The patient benefited from a plasmapheresis session and the evolution was characterized by a picture of hepatic encephalopathy made of behavioral disorders and biochemically, low prothrombin, low albumin, and major cholestasis.
Discussion
The pathophysiology of hepatic dysfunction in hyperthyroidism is multifactorial; it can be secondary to hyperthyroidism or associated with autoimmune liver disease, especially primary biliary cirrhosis and autoimmune hepatitis. In our patient, given the autoimmune context, especially vitiligo, and Graves' disease, it is very likely a non-known liver pathology, either primary biliary cirrhosis or autoimmune hepatitis, complicated by hepatic encephalopathy.
Conclusion
Graves' disease can be associated with several autoimmune disorders, including liver involvement. Screening for these disorders is important as they can affect the patient's prognosis.

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EP1068

A treasure hunt! An unusual presentation of benign thyroid tissue as cervical masses

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Introduction
Cervical masses in a patient with thyroid nodules raise the possibility of thyroid cancer with nodal metastases. Our case highlights the possibility of the rare presentation of benign thyroid tissue as a lateral neck mass in a patient with a previous history of thyroid surgery.
Case Description
A 66-year-old women with a past surgical history of partial left lobectomy for unclear reasons 30 years ago was referred by the surgeon for evaluation of thyroid nodules. She reported noticing palpable neck masses but didn't report associated heat/cold intolerance, palpitations, diarrhea, tremor, fatigue, skin/hair /sleep /weight/appetite changes. No associated neck pain, dysphagia, fever, URTI, or vaccination. No obstructive symptoms. No recent Biotin, herbal or over-the-counter remedies. No previous similar complaints, no family history of thyroid disorders. No radiation exposure and is postmenopausal. Vitals normal, BMI 22.7 Physical examination is significant for two right-sided rubbery, non-tender, mobile masses in right upper neck, palpable right thyroid nodules. The biochemical evaluation revealed normal CBC and CMP. -TSH 1.33IU/ml, FT4 1.06ng/dl -Thyroid US: two thyroid nodules 20x19x13mm,9x8x7mm and several small nodules in the right lobe and one Right mid jugular chain lymph node -US Neck mapping: R level III mid jugular: three lymph nodes measuring 4-5 mm, no fatty hila, other levels, and left side are normal -Lymph node Excisions of two right cervical lymph nodes showed fragments of benign thyroid tissue; no lymphoma, however, flow cytometry couldn't be performed due to lack of significant lymphoid population. -Thyroseq molecular test from the lymph nodes samples obtained was negative for genetic mutation -Repeat Thyroid US-Stable thyroid nodules -Repeat TFT after 2 months, TSH 2.180IU/ml, FT4 1.00ng/dl remained clinically, biochemically euthyroid.
Discussion
Ectopic thyroid tissue (ETT) is a rare phenomenon and usually occurs along the normal path of thyroid descent. There have been reports of thyroid tissue found in places such as the abdominal organs, pelvis, axilla, and thoracic cavity. It is, however, rare to find thyroid tissue within lateral neck masses. When thyroid tissue is found in a cervical lymph node, the suspicion of nodal metastasis of differentiated carcinoma of the thyroid should be high. In our case, FNAB of thyroid nodules, excision biopsy of lymph nodes, and a Thyrosequence molecular test were negative for malignancy. Our hypothesis is that in our patient with a previous history of thyroid surgery, the seeding of cells from thyroid tissue may be the possible mechanism

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EP1069

Thyroid pathology and hypofertility

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Introduction
Thyroid pathology is common in women of reproductive age. Evaluation of thyroid function is classically recommended in cases of recurrent abortion. The presence of dysthyroidism or antithyroid antibodies increases the risk of abortion. We report two observations of hypofertility related to thyroid pathology and discuss the therapeutic course.
Case 1
A 33 year old woman was referred for etiological investigation of recurrent abortion. She presented 3 successive abortions at 6, 8 and 12 weeks of amenorrhea respectively. The etiological investigation concluded to a Hashimoto's thyroiditis with FT4: 11.1 m IU/l and TSH: 13.46 m IU/l and strongly positive anti TPO antibodies. The diagnosis of latent hypothyroidism was retained. The patient was able to carry a pregnancy to term with a healthy baby under hormone replacement therapy.
Case report 2
A 35-year-old woman was referred for etiologic investigation of recurrent abortion. She had two in-utero fetal deaths at 12 weeks and 30 weeks of amenorrhea respectively. The thyroid workup was normal but the anti TPO antibodies were strongly positive. In the absence of a therapeutic consensus on how to deal with repeated abortions associated with positive antithyroid antibodies, our approach was to abstain with monitoring of the thyroid balance. The evolution was marked by the subsequent occurrence of two abortions and a patent hypothyroidism requiring hormone replacement. Hypofertility was attributed to a purely gynecological cause.
Discussion
Hypothyroidism is recognized as a cause of hypofertility. Several mechanisms have been put forward to explain the dys- or anovulation related to this pathology; these are essentially hyperprolactinemia, disturbance of sex steroids, etc. If not substituted, hypothyroidism exposes the patient to miscarriage, and fetal death in utero. Regarding thyroid antibody positivity in clinically euthyroid women, the majority of studies have found that the miscarriage rate is doubled in these women compared to women without antibodies. The hypothesis is that the presence of anti-thyroid antibodies reflects a

more generalized activation of the immune system. In this context, several studies report a decrease in the percentage of spontaneous miscarriages and preterm deliveries during treatment with immunoglobulins and levothyroxine in euthyroid women with anti-TPO antibodies.
Conclusion
The management of hypothyroidism during pregnancy is currently well codified, allowing the prevention of spontaneous miscarriage as shown in the first observation. However, the management of thyroid antibody positivity in clinically euthyroid women is still not consensual and the imputability of these antibodies remains to be demonstrated on large cohorts.

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EP1070

A Case of Myxoedema Coma Presenting as Suspected Angioedema with Confusion

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Background
Myxoedema coma although uncommon can be life-threatening in patients who are poorly compliant with levothyroxine replacement. Some of the precipitating factors include intercurrent respiratory infection, use of sedatives, and electrolyte imbalance such as hyponatremia(Wiersinga 2018). A 73-year-old man presented to the Hospital with face and tongue swelling, shortness of breath, and type 2 respiratory failure. His past medical history includes hypothyroidism, Obstructive sleep apnea syndrome (OSA), venous leg ulcers, Type 2 diabetes, prostate problems, and Atrial fibrillation. His current medications on table 2 below He initially received a CI esterase inhibitor for suspected angioedema and had some improvement in the Accident and Emergency Resuscitation room was transferred to the intensive care unit and intubated due to agitation and concerns about maintaining his airway. His blood test showed severe hypothyroidism likely due to poor compliance. He was treated with iv liothyronine(T3) and iv hydrocortisone. He was also treated for congestive cardiac failure. Chest X-ray showed bilateral pleural effusion. He developed hospital-acquired pneumonia for which he received iv antibiotics. His confusion improved with the improving thyroid function test table 1 below. He was discharged home on levothyroxine after prolonged hospital admission.
Discussion
Severe hypothyroidism presenting as myxoedema can lead to fatal outcomes. The mortality rate is around 30-60% (Wall, C 2000), and therefore early clinical diagnosis and timely treatment are important to ensure patient recovery and desired outcomes. The clinical manifestation of myxoedema coma is variable. Some of the clinical presentations include confusion, altered level of consciousness, hypothermia tiredness, generalized swelling, and constipation. The presented case had some of the above-mentioned clinical features and the swelling on his face and enlarged tongue were treated as suspected angioedema
Conclusion
Myxoedema coma is both a medical and an endocrine emergency. Early treatment using Liothyronine is important to get desired and better outcome for the patient. Ruling out Addisonian crisis and correcting hypothermia, hypotension, and other electrolytes imbalance contributes positively to patient care(Wiersinga 2018)

Table 1(Blood test results)

DATE	FT4	FT3	TSH
23/11/22	<0.5	1.8	30.90mU/l
29/11/22	5.5	1.8	15.5pmol/l

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EP1071

Transverse Myelitis and Covid-19 Disease in A Patient with Hashimoto's Thyroiditis

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Introduction
The SARS-CoV-2 virus has caused the recent pandemic. Most affected patients have gone through a rather mild disease. However, some of the patients have gone through a severe illness requiring admission to an acute care unit. Some survived while others succumbed to the disease. In some patients the SARS-CoV-2 infection was characterized by neurological manifestations. One of these is transverse myelitis thought to be caused either by the virus itself as the SARS-CoV-2 virus may be neuroinvasive or by an autoimmune reaction due to molecular mimicry between the viral and host proteins.
Aim
The aim was to describe the case of a male patient with Hashimoto's thyroiditis who developed transverse myelitis in the course of COVID-19 illness.
Case description
The case of a 52 year-old male patient is described. The patient presented with Hashitoxicosis approximately 15 years ago at the age of 37 years. TSH was 0.01 μIU/ml, anti-Tg and anti-TPO antibodies were positive, while a thyroid ultrasonogram revealed loss of homogeneity of the thyroid parenchyma. Unimazole was administered. During the course of the disease the patient developed hypothyroidism and thyroxine was administered. Approximately a year ago he presented with COVID-19 disease and a rather severe illness. The patient was admitted to a COVID-19 department. During hospitalization he started to feel numbness in the lower extremities and subsequently the lower extremities were paralyzed. Transverse myelitis was diagnosed and prednisolone was administered. Over the course of two months prednisolone was tapered and the patient improved. During the course of a year the patient improved substantially and is now in a program of rehabilitation. He is able to walk independently without the use of walking aids.
Conclusions
Transverse myelitis in the course of COVID-19 disease has been described. The disease may be due to the virus itself, as it may be neuroinvasive or to an autoimmune reaction due to molecular mimicry, i.e. due to the homology of amino acid sequences of the viral proteins to human amino acid sequences. Thus, an immune reaction to the SARS-CoV-2 virus leads to an immune reaction to proteins of the human host and the development of clinical autoimmune disease. The SARS-CoV-2 virus is neuroinvasive and may have led to the development of transverse myelitis. Alternatively, the SARS-CoV-2 virus may be a virus which leads to autoimmunity and may have led to an autoimmune reaction in a vulnerable host, as the patient described herein.

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EP1072

Unusual Warthin-like variant of papillary thyroid carcinoma associated with Hashimoto's thyroiditis

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Warthin-like variant of papillary thyroid carcinoma is a rare histologic variant of PTC; they resemble Warthin tumor of salivary gland, frequently associated with lymphocytic thyroiditis. There is scarce literature available regarding this tumor.
Clinical case
In August 2019 a 51-year-old female patient sought consult because she complained of constant pain in the anterior surface of the neck. Medical background: arterial hypertension, she had no history of family thyroid illnesses. On examination, she had a 2 cm painless nodule in the left thyroid lobe, with no lymph nodes. Ultrasonography: right lobe was measuring 45x20x21mm with multiple spongiform nodules, the largest: 16x9 mm; left lobe: 51x20x25 mm with a 19x17x17mm hypoechogenic nodule, with irregular margins, microcalcifications and minimal vascularization. In November 2019 ultrasound-guided FNA: nodule in right lobe: Bethesda II, nodule in left lobe: Bethesda VI: scattered cells and groups of cells with nuclear overlapping, elongated cells, anisokaryosis, 1-2 prominent nucleoli, intranuclear cytoplasmatic inclusions. There were two probable diagnoses: medullary thyroid carcinoma vs. an infrequent variant of papillary carcinoma. Hormonal laboratory: normal TSH, FT4 and calcitotin, negative TPO and antithyroglobulin antibodies. In January 2020 a total thyroidectomy and lymph nodes removal of region VI was performed. Pathology report: unifocal Warthin-like variant of papillary carcinoma of 0.7x0.7 cm, without lymphatic emboli, perineural and extra-thyroid invasion, lymphocytic thyroiditis in the remaining tissue. Region VI lymph nodes: 1/7 positive micrometastasis of papillary carcinoma (<2 mm) without capsular invasion.

Intermediate risk of recurrence, TNM: T1b, N1a, Mx. Under levothyroxine treatment: TSH 0.15 mUI/ml, thyroglobulin (TG) 0.04 ug/dl and negative antithyroglobulin antibody. Because of COVID-19 pandemic, treatment with 100 mCi radioiodine could be performed in October 2020 under recombinant TSH; whole body scan (WBS): positive in thyroid lodge and in the right region of the neck. Six months later, a neck ultrasonography showed a 11 mm adenopathy with cortical irregularity in III cervical region; a FNA was negative for neoplastic cells and thyroglobulin measurement in the needle washout after FNA was <0.1 ug/dl. In more than 3 years of follow-up, the patient had negative WBS, cervical ultrasonography and normal levels of thyroglobulin.
Conclusion
We presented a patient with a rare variant of papillary thyroid carcinoma associated with Hashimoto's thyroiditis with negative serum thyroid antibodies. The patient had excellent response to the treatments in more than 3 years of follow-up. We need a longer follow-up to define the real risk of this type of thyroid cancer.

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EP1073

Tuberculous lymphadenitis with the appearance of thyroid carcinoma metastasis

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Tuberculosis (TB) is a disease that affects all organs and progresses with a wide variety of clinical manifestations. Cases of extrapulmonary tuberculosis (EPTB) are particularly difficult to diagnose because of its atypical course.
Case
A 32-year-old female patient was evaluated in our clinic with the complaint of localized swelling in both supraclavicular regions (ScR) for one and a half months. There were no fevers, cough, or weight loss symptoms present. Ultrasonography showed approximately 6x6 mm calcified nodule in the left thyroid lobe and lymphadenopathy (LAP) of 3.2x2.4 cm in the left supraclavicular region (ScR) and 2.1x2 cm in the right ScR. A clinical diagnosis of metastasis of thyroid carcinoma or lymphoma were considered. In her family history, it was learned that her mother had TB and received treatment for 6 months. Hemoglobin 9.5 g/dl (11.7-15.5), the white blood cell count was 5,100 uL (4,4-11,3), erythrocyte sedimentation rate (ESR) was raised 1st hour 43 mm ($<$ 20), c-reactive protein of 8.2 mg/dl (<5). The results were negative for hepatitis markers, human immunodeficiency virus, toxoplasmosis, brucellosis and syphilis. Quantiferon-tb gold test was negative. Fine needle aspiration (FNA) cytology to the left thyroid lobe and left supraclavicular lymph nodes (ScLN) revealed epithelioid cells and necrotic material forming granulomas and lymphocytes. Thyroid nodule aspiration report: Atypia of undetermined significance. The real-time polymerase chain reaction (RT-PCR) test and Ziehl-Neelsen staining of the biopsy sample taken from the lesions in ScR were negative. No TB compatible lesion was found on computed tomography scan of the lung. Considering the pathology result and family history, tuberculous lymphadenitis was considered and 4-antituberculosis treatment was started. In the presence of palpable lymphadenopathy in countries where TB is common, TB should be considered in the etiology. TB affecting primarily ScLN is uncommon. In absence of systemic signs and symptoms, as in our case, it can be difficult to diagnose TB.
Key words
Tuberculous lymphadenitis, extrapulmoner tuberculosis, thyroid nodule

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EP1074

Squamous cell carcinoma of the larynx associated with thyroid carcinoma: a case report

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Introduction
The discovery of thyroid cancer during surgery for another malignant disease of the upper aerodigestive tract is rare. We report the case of a man presenting squamous cell carcinoma (SCC) of the larynx associated with papillary thyroid carcinoma (PTC).
Case presentation
A 68-year-old patient with history of cigarette smoking underwent total laryngectomy for laryngeal cancer associated with subglottic extension. Hemithyroidectomy on the lesion side was performed. On histology, SCC of the larynx and PTC were documented. Continuing to total thyroidectomy was decided secondarily and the other thyroid lobe was hyperplastic without signs of malignancy. The patient then received external radiotherapy as adjuvant therapy to surgery for his squamous cell carcinoma.
Discussion/Conclusion
Thyroid carcinoma found incidentally during treatment of SCC of the larynx is a rare event with very few cases reported in the literature. It is most often an incidental histological finding. The prognosis depends on the squamous carcinoma which therapeutic management is established. There is no well-coded management for combined thyroid and laryngeal cancers. In our patient, totalization surgery and external radiotherapy were performed as the only complement therapeutics. This was justified by the absence of poor prognostic factors for papillary thyroid carcinoma.

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EP1075

A vesicular carcinoma of the thyroid on Graves' disease: a rare association

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Introduction
The occurrence of vesicular carcinoma in Graves' disease is exceptional. It is most often a papillary carcinoma rarely vesicular. We report the case of a vesicular carcinoma discovered at the anatomopathological study of a total thyroidectomy in a patient followed for Graves' disease.
Observation
This is a 61-year-old female patient with type 2 diabetes, on SGLT2 inhibitor. There isn't any family history of thyroid cancer or exposure to radiation in the cervico-thoracic region. Consulted for pelvic girdle myopathy with thyrotoxicosis. The biological assessment showed a TSH of 00 uUI/ml, an LT4 elevated twice the normal value, positive anti TSH receptor antibodies at 21 IU/l, and on ultrasound a thyroiditis appearance with a left lower lobar nodule 3 of 20.4*24.3*22 mm classified EUTIRADS 3 and a right lower lobar nodule of 10.2*6.3 mm classified EUTIRADS 3. Thyroid scintigraphy showed an aspect in favour of Graves' disease associated with a hypo-captant left lower lobar nodule. The patient received synthetic antithyroid drugs until euthyroidism was obtained, then she underwent a total thyroidectomy.. Histology concluded to a vesicular micro carcinoma of the thyroid of 7mm in diameter with capsular breakthrough and without vascular emboli. The patient did not receive iodine 131, simple monitoring with L-thyroxine inhibitor treatment were indicated.
Conclusion
The association of Graves' disease and vesicular carcinoma remains rare but the discovery of a thyroid nodule during surveillance or even at diagnosis constitutes a predictive element requiring a careful search for malignancy as illustrated by our clinical case.

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EP1076

Papillay microcarcinoma in patient with graves' disease

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Introduction
Patients with Graves' disease are at a 2.5 times higher risk of developing thyroid cancer than the general population.

Objective
We report here a case of a papillary microcarcinoma discovered in patient with graves' disease.
Case report
This report is about a 51-year-old woman treated with anti-thyroid drugs and β blockers for Graves' disease. Cervical ultrasound found an enlarged, hypervascular thyroid gland with a 10 mm nodule classified EUTIRADS 5. Indications for surgery were: failed medical therapy after 3 years of treatment and concomitant suspicious thyroid nodule. The patient underwent total thyroidectomy. Intraoperative examination suggested a papillary thyroid carcinoma. A central neck dissection was performed. Histologic exam confirmed the diagnosis of papillary thyroid carcinoma associated with Graves' disease. The patient underwent ablative radioiodine therapy. After 9 years of follow-up, she had no recurrence.
Conclusion
Over 85% of thyroid cancer in patients with GD was papillary thyroid carcinoma, although other histologic types including follicular, medullary, and anaplastic carcinoma could be found in some studies. Patients with GD tend to have microcarcinomas Thyroid USG can identify more thyroid nodules or cancers in patients with GD, compared with palpation or radioactive iodine scintigraphy.

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EP1077

surprise or evil hidden behind a toxic thyroid nodule: about a case

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Introduction
Thyroid TB is rare even in endemic countries, and diagnosis is often delayed by atypical presentation and clinical latency. Rarely, if ever, does a tumor and infection form in the same thyroid nodule We report the case of a subject who was followed for a hot nodule and who was found to be both thyroid tuberculosis and tumor damage.
Observation
This is a 59 year old patient vaccinated against BCG, with no histrory of pulmonary or extrapulmonary tuberculosis, followed by atrial fibrillation on anticoagulant therapy. Treated for a few months for hyperthyroidism on a toxic hot nodule confirmed by radionuclide imaging. After laboratory euthyroidism was achieved with synthetic antithyroid medicinal products, the patient underwent a total thyroidectomy. The definitive pathological examination had noted epiteloid and gigantocellular follicles with the presence of caseous necrosis, concluding with thyroid tuberculosis; as well as the presence within the same nodule of an oncocyte tumor with a potential of uncertain malignancy. The clinical and paraclinical examination did not reveal any other site of tuberculosis, thus being a primary thyroid disease The patient was placed on anti-bacillary treatment for a period of 6 months
Discussion
The hot nodule, unlike the cold nodule, is generally a benign nodule with a low risk of malignant degeneration, this risk is far from being zero and approved by many authors but the coexistence within the latter of tuberculosis and a tumor is rare, even exceptional. Tuberculosis associated with a thyroid tumor is rare but can be common in immunocompromised patients. In the literature, several cases of a combination of tuberculosis and thyroid tumor have been reported. The causal relationship was demonstrated by a meta-analysis between pulmonary tuberculosis and lung cancer with a 74% risk of progressing to lung cancer after diagnosis of pulmonary tuberculosis. So far no studies have been performed that can demonstrate the same causal relationship for thyroid tuberculosis and neoplastic risk, although the relationship appears to be consistent.

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EP1078

Clinical case: I131 resistant follicular thyroid carcinoma

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Introduction
Follicular thyroid carcinoma (FTC) is the second most common thyroid tumor and accounts for about 5-10 % of all thyroid cancers. As FTC often retains the ability to concentrate radioactive iodine (I^{131}), tumor may be responsive to I^{131} therapy. However, about 60-70 % of all metastatic thyroid cancers are resistant to I^{131} and has a poor prognosis with 10-year survival rate of 10 % and the average life expectancy 3-5 years after diagnosis.
Case
A 64-year-old man was admitted to the Hospital of Lithuanian University of Health Sciences Kaunas Clinics for thyroidectomy due to thyroid follicular carcinoma pT3NxMx. Levothyroxine replacement therapy and I^{131} therapy were indicated. Four years later, patient was diagnosed with follicular thyroid carcinoma metastasis to the right III rib and S2-3 vertebra. Surgical treatment and I^{131} therapy were ineffective. After a few years, bone pain intensified, but ultrasonography (US) and computer tomography (CT) denied the possibility of relapse so the treatment with Denosumab was started. One year later, CT revealed a pathological lymph node between the right kidney and v. cava inferior - stereotactic radiation therapy was performed to the pathological lymph node. Patient complained about numbness in the buttocks, anal fissure, neck lump and weight loss.
Diagnostic tests
Chest, abdomen and pelvic organs CT: Pathological lymph node had increased up to 1,6 cm between the right kidney and v. cava inferior. A 6,7 cm solid mass was observed in the sacrum.
Thyroid US
A 2,2 x 1,3 x 2,6 cm of hypoechoic, non-homogeneous tissue with microcalcinates in the post-operative area was observed. There were no pathological lymph nodes in the neck.
Microscopic examination:
Biopsy of sacral solid mass identified follicular thyroid carcinoma metastasis. Fine needle aspiration biopsy of the neck lump revealed Hurthle cell neoplasia.
Treatment
Systemic treatment with Lenvatinib was initiated. A positive effect is observed after V courses of Lenvatinib, sacral and neck tumor masses have decreased. Lenvatinib has caused transient skin lesions and mild gastrointestinal disorders, treatment is continued.
Conclusion
Resistance to I^{131} is usually associated with higher mortality rate so that precise multiple imaging tests of the targeted organs with possible metastasis and molecular testing are important for appropriate management of the disease.

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Late Breaking

EP1079

Evaluation and treatment of cardiovascular risk factors in patients with adrenal insufficiency

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Introduction
Patients with adrenal insufficiency (AI) are known to have a higher cardiovascular risk (CVR) than the normal population. In particular arteriosclerosis, coronary heart disease, arterial hypertension, hyperlipoproteinemia as well as metabolic disturbances contribute to the increased morbidity and mortality. Aim of this study was to evaluate known cardiovascular risk factors as well as the quality of care by the treating physicians.
Material and Methods
To this end a questionnaire evaluating cardiovascular risk factors was handed out to all participating AI patients. In addition, we screened all medical records for CVR factors and documented the treatment initiated. Statistical analysis was performed by SPSS.
Results
In total, 363 AI patients were included in the study. 294 of these patients were found to have one or more cardiovascular risk factors. Although 51 patients suffered from diabetes mellitus, 2/3 still had increased HbA1c values. With respect to hyperlipoproteinemia, only 1/3 of the AI patients reached values in the normal range ($n=31$). 105 patients were diagnosed with arterial hypertension, of these 26 patients still showed increased values in the outpatient setting. The data shows that 51 patients have a diagnosis of Diabetes mellitus and 30 of them still have high HbA1c values. Furthermore, of the 85 patients with hyperlipoproteinemia only 31 have the blood fat in the normal range and 38 still have high values. For 16 not all of the blood fat values existed. Of 105 patients with hypertension, 44 still have a higher blood pressure.
Conclusion
Our study demonstrates (1) the increased CVR risk in patients with AI, leading to increased morbidity and mortality, (2) AI patients are inadequately monitored and

treated for CVR factors, thus having a higher risk of suffering from a cardiovascular event, (3) treating physicians should be aware of this risk to minimize complications where possible

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EP1080

Gitelman syndrome, a rare disease: case report

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Introduction
Gitelman syndrome(GS) is a salt-wasting tubulopathy characterized by renal potassium wasting, hypokalemia, metabolic alkalosis, hypomagnesemia, hypocalciuria and hyperreninemic hyperaldosteronism. It is caused by the mutation of genes encoding sodium chloride (NCCT) and magnesium transporters in the thiazide-sensitive segments of the distal nephron (SLC12A3 and TRMP6 gene). GS is a rare autosomal recessive disease with a prevalence of only 25 cases per one million population.
Case report
A 23-year-old girl diagnosed with Hashimoto thyroiditis with hypothyroidism, polycystic ovarian syndrome, short stature due to SGA (2000 g at 38 wks, twin pregnancy), treated with recombinant GH during childhood, presented for paresthesias of the hands, nausea, dizziness, and acne. Her clinical features were short stature (T = 154 cm) and low BMI (15.61 kg/mp). The biological assessment revealed persistent hypokalemia ($<$ 2.9 mmol/l), hypomagnesemia ($<$1.34 mg/dl), hypochloremia with a normal sodium and bicarbonate level, normocalcemia (9.13 mg/dl) with hypocalciuria (43 mg/24 h). Hormonal profile: normal thyroid function tests with levothyroxine replacement, hyperreninemic (281 uUI/ml, normal values: 2.8-39), hyperaldosteronism (35.2 ng/dl, normal values 1.76-23.2). The hepatic and renal functions were normal; she was also normoglycemic. The suspicion for Gitelman Syndrome was confirmed by the genetic testing, which showed heterozygosity for SCL12A3 gene mutation. Due to the absence of symptoms, her potassium and magnesium serum levels were not assessed periodically during childhood, and the diagnosis was raised at about 16 years. Her twin sister has average stature and no potassium or magnesium imbalance. Supplementation with oral potassium chloride of two grams per day and oral magnesium chloride 500 mg per day was started but with a slow improvement of biological parameters. Spironolactone treatment does not ameliorate potassium levels as in others hypopotasemia disorders but was mentained due to associated acne.
Discussion
Gitelman syndrome is a condition that may remain asymptomatic or present with mild or nonspecific symptoms. Phenotypic variability and potential severity are also seen in genetically confirmed GS patients, but many patients are not tested, with genetic testing that is not widely available and expensive. The primary differential diagnosis of GS is with Bartter syndrome, especially type III. Treatment is symptomatic and life-long to prevent cardiac arrhythmias and dehydration; it includes supplementation with potassium chloride (with better absorption) and magnesium replacement (organic salts are preferred). Magnesium replacement should be considered first because the repletion of magnesium will facilitate potassium repletion.

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EP1081

Cushing Syndrome Due To Acth-Secreting Pheochromocytoma: A Case Report

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Introduction
The most frequent causes of ACTH-dependent Cushing's syndrome are of pituitary origin and, less frequently, due to ectopic secretion of bronchial carcinoid, small cell lung cancer, and neuroendocrine tumors; it is rarely caused by an ACTH-producing pheochromocytoma.
Methodology
We present a case of a 44-year-old female with a history of poorly controlled type 2 diabetes, hypertension, and long-standing obesity with no genetic predisposition or typical Cushingoid features who was initially admitted due to edema in both legs and hyperglycemic decompensation. On arrival, analysis showed she presented hypokalemia and hyperglycemia, in addition to clinical hypertension that was difficult to control and altered behavior without history of previous psychiatric pathology. After a full-body CT scan incidentally revealed suprarenal damage, we began a radiological study. Adrenal CT scans showed a 4 $\times$ 3.5 cm right adrenal nodule and MR imaging of the pituitary did not reveal an adenoma.
Results
After starting pharmacological treatment with ketoconazole, the subject continued to have severe symptoms of hypercortisolism. Therefore, etomidate was administered to inhibit corticosteroid synthesis, alpha blockade was used in the preoperative preparation, and right adrenalectomy surgery was performed. The anatomic pathology results were intermediate risk, moderately differentiated pheochromocytoma (according to GAPP risk stratification). The patient subsequently evolved favorably, with the high levels of cortisol, ACTH, and metanephrine initially found in her urine decreasing to normal levels.
Conclusions
Although this is an extraordinary case, a full examination must be completed anytime a suprarenal nodule is found, as it may be the result of a ACTH-secreting pheochromocytoma and quick diagnosis and treatment are crucial.

Biochemical tests

Plasma levels	24-h urinary measurement
Basal cortisol 114.6 μg/dl (4.0 - 20.0)	Cortisol excretion 25199 μg/dl (0 – 134)
ACTH 215 μg/dl (7-62)	Normetanephrine 1145 μg/24h (0 – 444)
	Metanephrine 756 μg/24h (0 – 341)
	Epinephrine 32 μg/24h (0-18)
	Norepinephrine 262 μg/24h (0-7)

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EP1082

Pheochromocytoma presenting with multi-system crisis during endoscopic procedure: a case report

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A 45-year-old female patient with diagnosis of hypertension was admitted to Acibadem University Hospital for colonoscopy due to perianal abscess and rectovaginal fistula. She had been diagnosed with hypertension for 7 years and had been using 3 different classes of antihypertensive drugs. Intermittent hypertensive attacks and hospitalization for myocarditis history was documented. During anesthesia induction for colonoscopy her condition acutely worsened and she became hemodynamically unstable. She developed acute respiratory distress and was transferred to the intensive care unit. On physical examination, she was conscious, tachypneic, hypoxic and had wheezing under 15 lt/min oxygen support. Vital signs were; heart rate:150 bpm, respiratory rate: 32/minute, blood pressure:140/70 mmHg. Bilateral diffuse widespread infiltrates were seen in the chest radiography. Echocardiography demonstrated 30% ejection fraction. Blood gasses analysis revealed severe metabolic acidosis and hypoxia. She was put on non-invasive mechanical ventilation support. Arterial hypoxia persisted hence she was intubated. Due to insufficient response to diuretic therapy and multiorgan dysfunction syndrome she was put on continuous veno-venous hemodiafiltration (CVVHDF) and arteriovenous extracorporeal membrane oxygenation (ECMO) respectively. After 6 days of ECMO support, ejection fraction increased to 40%. Considering her clinical findings being suggestive of pheochromocytoma, radiologic and laboratory tests were ordered. Abdominal computed tomography (CT) revealed an 86x76 mm sized left adrenal mass. Levels of plasma metanephrines (179.5 pg/ml) (reference $<$90 pg/ml) and plasma normetanephrine ($>$4800 pg/ml) (reference $<$200 pg/ml) were determined. Gallium-68 DOTATATE PET/CT imaging revealed increased uptake on the mass (SUVmax: 43). Preoperative antihypertensive preparation was done with doxazosin and metoprolol. Then she underwent left adrenalectomy, splenectomy, left nephrectomy and cholecystectomy. Postoperative pathology confirmed diagnosis of pheochromocytoma. During weaning from mechanical ventilation, it was discovered that she developed polyneuropathy. EMG results were compatible with critical illness neuro-myopathy. Intravenous immunoglobulin (IVIG) therapy for 5 days was given. Plasma metanephrine levels returned to normal level post-operative 2 weeks later and she didn't need any antihypertensive drugs.

The patient was subsequently discharged, and has remained stable 1st year follow-up.

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EP1083

Abdominal extraadrenal paraganglioma: review of the literature and report of 3 cases

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Extraadrenal paraganglioma is a rare tumor. The clinical and pathological findings of patients with abdominal localization paragangliomas (perihepatic, paraaortic, interaortocaval and retroperitoneal) are described. Its characteristics and diagnostic imaging are analyzed, as well as its therapeutic management. Between January 2021 and January 2022, 3 patients with extra-adrenal paragangliomas were diagnosed, all of them women. The age of our patients was 26, 57 and 67 years. The location of these tumors was at the para-aortic, inter-aortocaval, retrocaval and perihepatic level; one of the cases also presented cervical paragangliomas, with a size of the lesions ranging from 13 to 30 mm. We reviewed the clinical data. In all cases, the paragangliomas were detected as an incidental finding in imaging tests performed for another reason, although re-examining the predominant symptoms were tinnitus, sweating, tremor and headache, only one of the cases presenting hypertensive crises. One patient presented with concomitant bilateral adrenal hyperplasia/adenomas, with incomplete dexamethasone braking, but with normal ACTH and cortisol, probable hypercortisolism (Cushing's syndrome). Metanephrine levels in 24-hour urine and catecholamines in blood were estimated in all cases, with elevated levels in one of the cases (coinciding with the hypertensive patient), with normal levels in the rest. The lesions were initially detected by computed tomography and a study was completed with 113I-MIBG scintigraphy and DOPA PET-CT in all of them. In addition, a genetic study was requested in all patients (kif-1b, MAX, NF1, PRKAR1A, RET, SDHA, Af2,B,C,D, TME127, VHL) with negative results. All cases were evaluated by Endocrinology, with a prescription of premedication with Doxazocin prior to surgery. All but one patient underwent surgical treatment. The case associated with carotid glomus is pending evaluation by surgery for excision. The preoperative diagnosis of non-functioning abdominal paragangliomas is difficult, although they should be suspected in patients with hypertension or compatible symptoms. The 3 reported cases were found in the usual locations: paraaortic, interaortocaval, retrocaval, and perihepatic. All the patients except one had multiple tumors at the abdominal level, in addition to carotid glomus in one of the cases. Resection is the treatment of choice with prior initiation of alpha-blocker medication. These patients should follow a multi-disciplinary approach.

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EP1084

Primary adrenal lymphomas, a race against time

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Introduction
Primary adrenal lymphomas (PAL) are extremely rare and constitute 0.5% of all adrenal tumors. The number of cases described is approximately 70 cases [1] and It is bilaterally manifested in approximately 70% of cases [2]. The diagnosis is made on histological features, as there is no specific symptoms. Treatement is based on chemotherapy and prognosis is usually poor. We report two cases of bilateral PAL.
Cases
First case: A 63-year-old woman, admitted for exploration of a bilateral adrenal mass discovered on CT-Scan requested after a 3 week history of asthenia, weight loss, vomiting and abdominal pain. Her medical history comprised hypertension and and stroke. Clinical examination revealed no signs of hypersecretion. Biology showed elevated lactate deshydrogenase(362 UI/l) and β-2 microglobulin levels (4.97 mg/l). On imaging, there was large adrenal masses measuring 7 cm on the right and 9 cm on the left side with 32UH of spontaneous density and signs of vascular infiltration. CT-guided biopsy concluded on diffuse large B-cell lymphoma. Chemotherapy treatment was decided, unfortunately, the patient died before starting treatement.
Second case
A 52-year-old man, with a medical history of diabetes mellitus, was admitted for exploration of a deterioration of general condition. Adrenal insufficiency was confirmed by low cortisol level and required hydrocortisone replacement therapy. β-2 microglobulin level was elevated (3.34 mg/l). Abdominal CT-scan revealed 2 adrenal masses measuring 7 cm on the right and 3 cm on the left side with a spontaneous density of 35UH infiltrating the stomach greater curvature, the pancreas tail and The upper pole of the left spleen. The biopsy had shown a Diffuse large B-cell lymphoma. Chemotherapy was decided and patient is still receiving courses.
Conclusion
The prognosis of PAL is usually poor, it grows progressively throughout the adrenal glands. Thus early diagnosis and treatment is the key to saving patients.
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EP1085

A case of Primary pigmented nodular adrenocortical disease in a young woman with arterial hypertension

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Primary pigmented nodular adrenocortical disease (PPNAD) is a rare form of ACTH-independent Cushing's syndrome (CS). Approximately 30% of patients with PPNAD are sporadic cases and the other are familial. We describe a case of a patient affected by PPNAD presenting with isolated arterial hypertension. A 19-year-old black female patient was referred to the Endocrinology Unit in september-2021 due to severe arterial hypertension and fatigue. Previous clinical history was unremarkable and physical examination did not reveal typical signs of hypercortisolism. The echocardiogram revealed mild cardiac hypertrophy and antihypertensive treatment was started, but the subsequent laboratory tests revealed: normal potassium levels, increased midnight salivary cortisol levels (MSC 10-8.9-10.1 nmol/l n.v. <2.8), increased cortisol levels after both 1 mg and 8 mg dexamethasone suppression test (15 mg/dl, 20.1 mg/dl respectively), low plasma ACTH levels (1.5 ng/l; n.v.: 8-50) and increased urinary free cortisol excretion (81.5 mg/24h n.v. <43), with aldosterone and renin levels within normal ranges. Computed tomography (december-2021), showed a slight enlargement of the left adrenal gland with a 8 mm nodule however, adrenal scintigraphy documented the presence of a bilateral (131)I-norcholesterol, uptake. ACTH-independent CS was diagnosed and treatment with metyrapone was started (750 mg) in order to achieve disease control before surgery. Unfortunately, after a few weeks, the patient complained hypoadrenal symptoms as abdominal pain, nausea, and fatigue worsening even in the presence of normal morning cortisol levels, and the treatment was discontinued. The patient underwent left-sided laparoscopic adrenalectomy (october-2022). Histopathological examination confirmed typical features of PPNAD (multiple cortical solid black nodules of 0.4–2.5 mm). Perioperative hydrocortisone therapy was performed and replacement treatment with cortisone acetate was started before hospital discharge. At the last visit, three months after surgery, adrenal insufficiency was confirmed (morning basal cortisol 8 mg/dl with cortisol peak after Synacthen test 12 mg/dl), ACTH levels were still suppressed, and so were androgens and MSC (1.3 nmol/l). However, blood pressure control was still scarce and antihypertensive treatment was maintained. An extensive follow-up has been scheduled due to the high risk of recurrence. Genetic testing revealed a rare heterozygous missense PDE8B germline mutation, c.219G>C (p.Glu73Asp), inherited from her father who is normotensive and presents normal cortisol levels after 1 mg dexamethasone suppression test.

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EP1086

Hyponatremia and its prevalence in the outpatient setting

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Introduction
Hyponatremia is the most common electrolyte disorder and it affects approximately 5% of adults and 35% of hospitalized patients. Diagnostic and/or therapeutic challenge is given. It is defined by a serum sodium concentration of less than 136 mmol/l. Symptoms of hyponatremia range from mild and nonspecific to severe and life-threatening. Hyponatremia is classified as mild, moderate and severe and may be acute or chronic. Mortality and morbidity are significantly increased in patients with hyponatremia.
Material and Methods
About 46.700 medical records between Augusts 2012 and 2022 were screened in an outpatient endocrine department. In 136 cases hyponatremia was found with an overall prevalence of 0.3%. Due to missing data, 40 patients had to be excluded from statistical analysis. Patients were analyzed with respect to age, sex, BMI, pre-existing conditions, medication, type and degree of hyponatremia and random finding of hyponatremia. Symptoms, therapy and serum sodium levels before and after treatment were assessed. To evaluate the prevalence of hyponatremia in the outpatient setting and identify specific risk factors.
Results
Females (79.2%) were more affected than males. Afflicted patients had a mean age of 71 years. With respect to severity, 19.7 % of patients had mild, 43.9% moderate and 36.4% severe hyponatremia. 97% of patients complained symptoms like nausea, vomiting, fatigue and dizziness. 59.1% of patients were diagnosed with SIADH with 6.1% also having a post op SIADH. In 25.8% cases the origin could not be clarified in the course of the disease. Hypervolemic or hypovolemic hyponatremia was found in 9% of the patients. Regarding known risk factors such as diuretic use, previous cardiological disease or nephrological preconditions we found no notable differences compared to patients without hyponatremia. Although women are more likely to develop hyponatremia, gender did not seem to play a role in the severity of the disease. The presence of incidental finding probably had an influence on the degree of hyponatremia. Conventional treatment (drinking restriction, adaptation of the medication schedule, modification of diuretics and/or tolvaptan therapy) led to a meaningful improvement in 74% of patients.
Conclusion
The number of outpatient cases was noticeably lower than the average number of hospitalized patients. However, in almost 25% of the affected patients, the origin could not be found. Guidelines and therapies used in the hospital also showed a noticeable improvement in this patient group. We hypothesize, that quick treatment may reduce the mortality and morbidity of outpatients.

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EP1087

Unusual case of iatrogenic adrenal insufficiency related to corticosteroid eye drop usage

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Corticosteroids have been widely used within the management of wide spectrum of conditions. It is well known that long-term use of exogenous glucocorticoids leads to the suppression of the hypothalamic– pituitary–adrenal axis. Even a 5-day course of oral high-dose steroid therapy can cause adrenal suppression. Similarly, high-dose steroid therapy - administered intranasally, inhaled or applied topically to skin can cause adrenal suppression. Depending on administration form, the percentage of patients with adrenal insufficiency varied from 52.2% for intra-articular corticosteroids to 4.2% for nasal corticosteroids. Hence topical route is preferred over oral or parenteral route and administered for shortest possible duration. It is extremely unusual to develop adrenal insufficiency with corticosteroid eye drop usage. In fact, a study specifically designed to establish whether hypothalamic-pituitary-adrenal axis suppression is possible secondary to long-term topical ophthalmic corticosteroid use in patients undergone penetrating keratoplasty (PKP) found no evidence that using continuous long-term corticosteroid eye drops after PKP experienced adrenal suppression. I present a young boy, born with Bilateral Peter's anomaly, a condition is characterized by central, paracentral, or complete corneal opacity as well as Bilateral congenital glaucoma. He was treated glaucoma tube implant surgery, Bilateral penetrating keratoplasties (full thickness corneal transplants) followed by Dexamethasone 0.1% eye drops twice a day to prevent rejection. By age 9 yrs, he displayed Cushingoid features and possibility of adrenal insufficiency was raised. Hence dexamethasone eye drops were withheld for 1 week. In the interim, Parents were educated regarding possibility of developing adrenal crisis and provided with emergency hydrocortisone supply. One week later, short synacthen test was arranged which revealed Serum Cortisol of < 10 nmol/l at at 0,30 and 60 minutes. His ACTH $<$ 5 (ref 7.2 – 63.3 ng/l) and Adrenal Antibody was negative. Since then further assessment of hypothalamic–pituitary–adrenal axis have consistently revealed complete adrenal suppression. He continues to require dexamethasone eyes drops to treat his ophthalmic condition and is treated with hydrocortisone replacement therapy to treat his adrenal insufficiency.
Learning points
• Long-term use of glucocorticoids leads to the suppression of the hypothalamic–pituitary–adrenal axis which is known as glucocorticoid-induced or iatrogenic adrenal insufficiency.
• Possibility of iatrogenic Adrenal insufficiency should be considered in the differential diagnosis in all patients receiving long term corticosteroid therapy in any form. A thorough clinical as well medication history is of paramount importance in suspecting as well as arriving at the correct diagnosis.

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EP1088

Unconventional 21 hydroxylase block revealed by high blood pressure : about a case

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Introduction
Enzyme block is a rare disorder that can be discovered at birth by a severe, life-threatening disorder or in a more attenuated form in adulthood by a clinical picture of hyperandrogenism most often. The enzyme block most commonly suspected in high blood pressure is 11 B OH blockWe report the case of a young patient who was diagnosed with 21 hydroxylase enzyme block by secondary hypertension testing.
Observation
This is a 32 year old patient without any notion of familial hypertension or salt loss syndrome in the family, followed for hypertension for 8 years, i.e the age of 24 years on dual therapy and whose evolution was marked by hypokalaemia motivating an exploration in the sens of secondary high blood pressure. Endoctrine investigations revealed an adrenal mass of 3.5 cm, density >10 and a wach or relative 34% and without associated hyperplasia. The secretary balance related to the dosage of FLU, DOC, SDHA, SRAA as well as the DM strictly normal income. In addition, the patient is monitored for primary infertility with the use of IVF without conclusive results and in whom the examination does not find any manifest clinical biological androgenism. In this sense, the dosage of 17progestogen hydroxy is raised to 8 ng/ml as well as del4A raised to 1.6 ng/ml thus diagnosing late 21 hydroxylase enzyme block.
Discussion
21 hydroxylase block is the most common form and accounts for 80% of enzyme blocks, and diagnosis is usually made by measuring 17 progestogen hydroxy in the morning in the follicular phase with the progestogen test for amenorrhea. A value greather than 5 ng/ml makes it possible to make the diagnosis, which can be confirmed by the synacthene test with a valur required at 10 ng/ml in order to be able to confirm the latter. Treatment is with frenzator doses of hydrocortisone.
Conclusion
Late 21 hydroxylase enzyme block may be found in the less suggestive table, but should always be considered in the presence of primary or secondary infertility even in the absence of hyperandrogenism.

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EP1089

Influence of muscle mass and strength on bone mineralization with consideration of sclerostin concentration

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Introduction
Osteoporosis is a disease characterized by a decreased bone strength, as a result of increased bone porosity and impaired mineralization. According to the mechanostat theory, loads generated by the muscle mass and muscle strength, stimulate bone reconstruction.
Aim of the study
In our study, we investigated whether muscle strength and mass exert a significant effect on bone mineral density in young adult women. We also tested whether sclerostin concentration can be used as an indicator in the assessment of bone mineralization.

Methods
The study included 111 patients with transient menstrual disorders, in whom organic causes were excluded. The subjects had their anthropometric measurements taken, along with a laboratory analysis of hormonal status. Metabolic activity of osteocytes was assessed by serum sclerostin concentration, using an enzyme-linked immunosorbent assay (ELISA). Whole body and lumbar spine bone mineral density (BMD) as well as body composition (fat mass- FM, lean body mass – LBM, visceral fat -VF) were assessed by dual-energy X-ray absorptiometry (DXA). Muscle strength was assessed by measuring handgrip strength using a hand dynamometer.
Results
There was a significant positive correlation of left and right handgrip strength and all parameters expressing bone mineralization. Lumbar spine (L1-L4) BMD was also positively associated with the body mass components: fat mass, lean body mass and their ratio (FLR). In contrast, sclerostin levels in this study did not differ between groups with normal and reduced bone mineral density.
Conclusions
Assessment of muscle strength may be an indicator of decreased bone mineral density in young adult women. However, the utility of sclerostin in the clinical assessment of bone mineralization has not been demonstrated.

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EP1090

Systematic review of cardiovascular morbidity and mortality associated with primary hyperparathyroidism; does early surgical intervention improve the outcome?

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Introduction
Primary hyperparathyroidism is associated with numerous cardiovascular complications including hypertension, left ventricular hypertrophy and calcification of cardiac valves. However, guidelines from expert panels and NICE have not included cardiovascular complications as an indication of parathyroidectomy. This literature review will be focused on benefits of parathyroidectomy on cardiovascular complications of primary hyperparathyroidism.
Methodology
Literature search done through use of search engines goggle scholar, PubMed, Cochrane database, Medline and EmBase using PRISMA model. Initial database search revealed 79 studies. After applying exclusion and inclusion criterion, 43 studies were finalized for systemic review.
Results
Amongst the cardiovascular complications of 1HPT hypertension and LVH are most investigated in literature and evidence is relatively strong for hypertension and LVH compared to other cardiovascular complications. Evidence is relatively weak for coronary artery disease, serum lipid profile, endothelial vasodilatory dysfunction, calcification of cardiac valves, occurrence of cardiovascular events and cardiovascular mortality.
Conclusion
Although evidence for beneficial effects of parathyroidectomy on HTN and LVH is relatively strong, lack of well-designed multicenter randomized control trial seems to be the main obstacle for inclusion of this as part of parathyroidectomy criterion. However, there is a rationale on basis of evidence available to include Hypertension and LVH as possible indications. Consideration should be given for inclusion of echocardiogram at baseline and follow up of 1HPT patients managed conservatively.
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EP1091

Surgical treatment for Primary hyperparathyroidism in ederly patient

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Introduction
Primary hyperparathyroidism (PHPT) is the third most common endocrine disease, the incidence is greater in women (ratio 3-4:1) and the prevalence increases with age (1). Surgery is the only curative treatment and usually in elderly patients there is a delay or are not considered for parathyroidectomy due to perceived high operative risk or postoperative complications (2)
Clinical Case
A 84 year-old female patient was under treatment with Cinacalcet since the diagnosis of PHPT four years ago, at the beginning she was not considered for surgery due to her age and comorbidities (kidney disease, prefrailty stage). In the last year patient suffered a worsening of cognitive decline, affecting medication compliance and water intake, being admitted at the hospital with hypercalcemia of 16 mg/dl with neurological and kidney function impairment, after the administration of intravenous hydration, zoledronic acid and calcitonin, calcium levels went to normal. Surgery was done after outweigh benefits over the risks. The ultrasound and scintigraphy localized the parathyroid adenoma superior to the right thyroid lobe, intraoperative PTH levels decreased in more than 50% resulting in normal PTH and calcium levels, and the anatomy pathology confirmed adenoma. Although the patient was able to get discharged she had prolonged stay in hospital as consequence of nosocomial pneumonia and urinary tract infection.
Conclusion
Albeit there is risk for any procedure and an inverse association for parathyroidectomy in older patients (3), data have shown that surgery is safe in the elderly, improves the symptoms and quality of life (4). So surgery should not be ruled out as complications can come from that decision particularly in a patient with no adherence to medical treatment and improvement was not expected without parathyroidectomy.
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EP1092

Parathyroid Carcinoma – an uncommon endocrine malignancy

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Case history
A 62-year-old male presented with generalised weakness, decreased oral intake, increased lethargy and polydipsia. He had a background of type 2 diabetes, hypercholesterolemia, and was a heavy smoker. No family history of parathyroid disease, other disorders causing hypercalcaemia or other endocrine tumours.
Investigations
Initial blood results showed severe hypercalcaemia adjusted calcium 3.87mmol/l (2.2 - 2.55mmol/l), significantly raised PTH 61.8pmol/l (1.6 - 6.9pmol/l), normal serum phosphate, normal renal function with vitamin D of 77nmol/l He had not reported previous fractures or history of renal calculi. Localisation studies with neck ultrasound did not localise a parathyroid adenoma but showed a left thyroid spongiform nodule (U2). Subsequent Technetium99m (99mTc)-sestaMIBI-99 scan demonstrated a functional parathyroid adenoma in the upper left part of the thyroid.

Results and treatment
Due to multiple episodes of severe hypercalcaemia, he required frequent hospital admissions for intravenous fluids and intravenous bisphosphonates. He was temporarily started on Cinacalcet which was uptitrated to 90 mg four times daily to manage his hypercalcaemia whilst awaiting definitive management. Two months following his initial presentation he underwent parathyroid surgery, due to suspicion of carcinoma intra-operatively, he underwent a hemithyroidectomy. Histology report confirmed a 30 mm parathyroid carcinoma, GATA3 positive. Proliferation index indicated by MIB1 was less than 5% with no infiltration into the thyroid, or local lymph nodes. There was no evidence of metastasis on subsequent CT scan of chest, abdomen and pelvis. PTH and calcium normalised with no hypocalcaemia post operatively and resolution of initial presenting symptoms.
Conclusion:
Parathyroid carcinoma is an extremely rare disease accounting for less than 1% of primary hyperparathyroidism. This case demonstrates the challenge of pre-operative diagnosis due to the difficulty in distinguishing from benign disease, owing to the absence of reliable diagnostic criteria and initial presentation can be similar. It is essential to consider the diagnosis of parathyroid carcinoma in cases of severe hypercalcaemia with marked rise in PTH (often over 5 times the upper limit of the normal range). Unlike benign causes of hyperparathyroidism, parathyroid carcinoma has an equal prevalence in males and females, with a lower average age of diagnosis and is more likely to have concomitant renal and skeletal involvement. Most cases are sporadic however rarely it can occur in those with familial hyperparathyroidism. Further elucidation of the molecular pathogenesis of parathyroid carcinomas will enhance our understanding of this rare entity

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EP1093

Spontaneous remission of primary hyperparathyroidism postpartum

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Introduction
Primary hyperparathyroidism is a disorder, characterized by autonomous overproduction of parathormone resulting in hypercalcemia. The main cause is a parathyroid adenoma. Less common etiologies are parathyroid hyperplasia and carcinoma. Primary hyperparathyroidism during pregnancy is rare and the management could be challenging. Maternal and fetal/neonatal complications occur in more than 50% of the cases.
Patient
We report about a 38-year-old female, who was referred with hypercalcemia for further evaluation. The patient suffered from rheumatoid arthritis treated with prednisolone 2.5 mg/d. She reported no symptoms. Parathormone 12.1 pmol/l (1.6-6.9), albumin adjusted calcium (AAC) 2.59 mmol/l (2.1-2.55), phosphate 0.87 mmol/l (0.8-1.45), calciuria 9.7 mmol/d ($<$6.2), 25-OH-Vitamin D3 46.8 nmol/l (50-150) and 1.25-OH Vitamin D3 207 pmol/l (47.8-190) showed primary hyperparathyroidism. Ultrasound revealed no enlarged glands. Pregnancy occurred while under investigation. During pregnancy ACC remained stable at 2.7 mmol/l and parathormone at the upper normal range by 6.7 pmol/l. Repeated neck ultrasound during the second trimester was non diagnostic. No maternal or fetal complications occurred. Labor started spontaneous at 43 weeks. One month postpartum the biochemical markers were normalized. Six months after delivery secondary hyperparathyroidism due to vitamin D deficiency was shown.
Conclusion
Spontaneous resolution of primary hyperparathyroidism is rare, but is reported after infarction or hemorrhage of small parathyroid adenomas.

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EP1094

Abstract withdrawn

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EP1095

Effectiveness of empirical antibiotic therapy in diabetic foot infection in a Portuguese Center

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Introduction
Diabetic foot infection imposes a significant burden and is a major cause of non-traumatic limb amputation. Antibiotic therapy plays a crucial role in the management these patients. In our institution, empirical antibiotic therapy is tailored to the presence of risk factors for multidrug-resistant microorganisms. For patients without risk factors, empirical intravenous amoxicillin-clavulanate at a dose 2.2 g every 8h is used. For patients with risk factors such as previous hospitalization or antibiotic therapy in the last 3 months, or hemodialysis, empirical intravenous vancomycin and piperacillin-tazobactam (P/T) at a dose of 4.5 g every 6 hours is recommended.
Objective
To assess the adequacy of empirical antibiotic therapy recommended in our protocol in relation to microbial isolates.
Methods
We conducted a retrospective cohort study that included patients who were hospitalized for neuropathic diabetic foot infection on a tertiary refferal hospital between January 2020 and December 2022. Tissue specimens (biopsy or aspiration of purulent exudate) were aseptically collected from the ulcer for culture. Demographic, clinical, and microbiological data were collected.
Results
Fifty-one patients were enrolled in this cohort, 69% of whom were male, with a mean age of 58.9 ± 11.9 years, and 73% of whom had type 2 diabetes mellitus. Two-thirds of cases were classified as PEDIS 3, and one-third as PEDIS 4. Sixty-one percent of patients had risk factors for multidrug-resistance. A total of 108 microorganisms were identified (an average of 2.7 pathogens per patient). *S. aureus* was the most frequently identified pathogen (20%), and *P. aeruginosa* was the most frequent Gram-negative bacteria (10%). Fourteen percent of S. aureus and 58% of coagulase-negative *Staphylococcus* were methicillin-resistant, and 35% of *Enterobacterales* were resistant to P/T. All *P. aeruginosa* were sensitive to P/T. Overall, by applying our treatment guidelines, antibiotic coverage of the identified pathogens was achieved in 75% of cases (84% in patients with risk factors, and 60% in patients without risk factors
Conclusion
Not initiating broad-spectrum antibiotic therapy in all cases reduces the risk of antibiotic resistance emergence (at the possible expense of a lower percentage of initial empirical coverage in patients without risk factors for multirrestance). To avoid compromising patient outcomes, it is essential to collect samples for culture as early as possible. Our study highlights the high adequacy of empirical antibiotic therapy protocols that take into consideration risk factors for multidrug-resistant microorganisms, which ultimately improves the outcomes of these patients.

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EP1096

Subtypes of gestational diabetes based on indices of insulin sensitivity and insulin secretion

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Objectives
Some authors have defined subtypes within gestational diabetes (GD) based on the calculation, from glucose and insulin levels during oral glucose overload (OGTT), of indices of insulin sensitivity (Matsuda) and insulin secretion (Stumvoll). Powe *et al* [1] found that 30% of women with GD had predominantly low insulin secretion, 51% low insulin sensitivity and 18% both (mixed). The aim of this work is to analyze the correlation of these indices with other known parameters of insulin sensitivity and insulin secretion and the definition of GD subtypes in our population.
Material and Methods
We calculated the Matsuda and Stumvoll indices (at 120 minutes), from the data of 68 100 g OGTT for the diagnosis of GD (both basal, 1-hour, 2-hour and 3-hour glucose and insulin were determined) and correlated them with HOMA and C-peptide. Based on the 25th percentile of these indices in the non-GD population, we established cut-off points and defined the 29 GD patients as having predominantly low insulin sensitivity (Matsuda < 25th percentile), predominantly low insulin secretion (Stumvoll < 25th percentile), both, or neither.
Results
We found that both the Matsuda and Stumvoll indices correlated significantly inversely with HOMA and C-peptide, as well as with each other directly, both in the general population and in women with GD (Table 1).
Conclusion
Both the Stumvoll index and, mainly, the Matsuda index correlate well with HOMA, which is more widely used and easier to calculate. Contrary to that previously described by Powe *et al* [1], in our population the mixed GD group predominates, with a similar percentage of women with a predominance of low insulin secretion and a much lower percentage with a predominance of low insulin sensitivity.
1. Powe CE, Allard C, Battista MC, Doyon M, Bouchard L, Ecker JL, Perron P, Florez JC, Thadhani R, Hivert MF. Heterogeneous Contribution of Insulin Sensitivity and Secretion Defects to Gestational Diabetes Mellitus. Diabetes Care. 2016 Jun;39(6):1052-5. doi:10.2337/dc15-2672.

Table 1 Regarding GD subtypes, 3.4% presented predominance of low insulin sensitivity, 34.5% predominance of low insulin secretion, 41.4% both and 20.7% neither of them.

General population	HOMA	C-peptide	Stumvoll
Matsuda	r= -0.635 (P< 0.001)	r= -0.674 (P< 0.001)	r= 0.308 (P=0.011)
Stumvoll	r= -0.504 (P< 0.001)	r= -0.361 (P=0.003)	
GD	HOMA	Péptido C	Stumvoll
Matsuda	r= -0.689 (P< 0.001)	r= -0.793 (P< 0.001)	r= 0.472 (P=0.010)
Stumvoll	r= -0.544 (P=0.002)	r= -0.382 (P=0.041)	

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EP1097

Action of Ro 60-0175, 5-HT2C receptor agonist in the central nervous system, in obese and diabetic Wistar rat

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Background and AIMS
Obesity can be caused because of reduction in energy expenditure and /or increased caloric intake. Total calorie intake has increased in recent decades, and research and studies on eating behaviour have reported increased intake of foods rich in fats and sugars. Excess calories alone increase body weight and reduce insulin sensitivity, even in healthy individuals who are not obese. In addition, increased consumption of sugars and fats is associated with weight gain and the development of insulin resistance in humans. Many regulatory pathways for food intake, including those that use serotonin as a neurotransmitter, are affected by obesity or by hypercaloric diets leading to obesity. Summarizing the data known so far, it can be said that reduced serotonergic signalling and low availability of SERT are associated with hyperphagia and obesity. Because of these facts, it is important to know how brain serotonin mediation affects food behaviour.
Materials-Methods
Ro 60-0175 is a novel 5-hydroxytryptamine (HT)(2C) (serotonin) central receptor-selective agonist that we used in our study. We used forty Wistar rats separated in 2 groups- rats with obesity and diabetes and healthy rats (control group). Each of these groups was separated in other 2 - one with a daily intraperitoneal injection (i.p.) of Ro 60-0175 (for 1 mg/kg increasing till 3 mg/kg per day) and one without. In 4 weeks period, we were tracking blood glucose levels, insulin secretion and rats' weight.
Results
It was shown that after the application of Ro60-0175, the weight of the rats in the diabetic and obese group decreased by 5.5% (P< 0.05), and by 2.56% in the control group and no significant dynamic in the groups without daily intraperitoneal injection of Ro60-0175. In the diabetic and obese rats group in which Ro60-0175 was applied, we registered a reduction of hyperglycemia by 35.4% (P< 0.05) comparing the results before the start of using Ro60-0175, which is greater in the rats which reduce more body weight. The research also shows decreasing of insulin resistance by 42.1 % (P< 0.01) in diabetic and obese rats group using Ro60-0175.
Conclusion
Using Ro 60-0175 for the treatment of obesity and obesity-induced diabetes in male Wistar rats, Ro 60-0175 significantly reduces body weight hyperglycemia and peripheral insulin resistance. In the study was registered reducing of body weight not only in the obese and diabetic rats group but also in the control group

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EP1098

Assessment of the impact of glycemic variability on the duration of the perioperative period in patients with diabetes mellitus and purulent infection of the maxillofacial region

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Patients with diabetes mellitus (DM) are more likely to suffer from purulent infection, probably due to compromised immune response. Achieving target levels of glycemia is a prerequisite for the perioperative management of patients with DM. However, the specific parameters of glycemic variability, optimal glucose range for the effective treatment of purulent infection of the maxillofacial region have not been established yet.
Purpose
to assess the impact of compensation of DM on the perioperative period, the duration of hospitalization in patients with DM and purulent infection of the maxillofacial region.
Materials and methods
528 patients with DM were examined while undergoing surgical treatment from moderate purulent infection of the maxillofacial region (determined by the severity of intoxication, the extent of the lesion) for 2019-2022: with an average age of 62 ± 36 (men -245, women -283); duration of DM from 0 to 31 years. Conducted: assessment of the impact of various glycemic parameters on the hospital stay, the perioperative period.
Results
Upon admission, the level of prandial glycemia was 11.03 ± 5.79 mmol/l; postprandial glycemia - 14.37 ± 6.01 mmol/l, glycemic fluctuations throughout the day 3.54 ± 2.88 mmol/l. After correction of glucose-lowering therapy, prandial glycemia decreased to 8.46 ± 4.33; postprandial decreased up to 11.33 ± 4.57, while glycemic fluctuations during the day were 3.94 ± 2.98. Statistical data processing revealed that the level of post-prandial glycemia during the day has a maximum impact (19%) on the duration of hospital stay. The calculated model is U = 1.5X-8, where U - the days of hospitalization, x- the maximum level of glycemia, (P < 0.001). An increase in maximal postprandial glycemia by 1.0 mmol/l prolonges hospital stay by 1,5 days. The prandial levels of glycemia also effect the length of hospital stay by 10% (r2-0.10). Estimated model of days of hospitalization: U = 17-0.6X, where U- the days of hospitalization, x- level of fasting glycemia, the model is calculated with an accuracy of 95%. If maximum level of glycemia during the day is less than 12 mmol/l, the recovery time decreases up to 10 days.
Conclusions
1) The highest level of glycemia during the day is the most significant parameter affecting the perioperative period. 2) The optimal level of postprandial glycemia throughout the day should be less than 12 mmol/l in patients with DM and purulent

infection of the maxillofacial region undergoing surgical treatment. 3) When the level of postprandial glycemia increases by 1 mmol/l, the number of days of hospitalization increases by 1.5.

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EP1099

Associations of Pparg Gene Polymorphic Marker with Carbohydrate Metabolism in Patients with Prediabetes

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Purpose
To study the frequency of polymorphic alleles and genotypes of the PPARG (rs 1801282) gene and its effect on carbohydrate and lipid metabolism in patients with prediabetes.
Materials and methods
The object of the study were 60 patients (32% men, 68% women) with early disorders of carbohydrate metabolism (WHO criteria, 2009). The mean age was 44.3 ± 7.8 years. The average value of fasting glycemia - 5.7±0.42 mmol/l, the average level of glycated hemoglobin was 5.96±0.36%. The average value of BMI is 31.6±5.4 kg/m2. The control group consisted of 30 practically healthy people. Indices calculated: HOMA-IR, QUICKI, HOMA1-β. Investigated blood parameters (lipid spectrum, indicators of carbohydrate metabolism). The quantitative determination of C-peptide, insulin, ghrelin, leptin in plasma was assessed by flow fluorometry on laser automated analyzer Bio-PlexProHuman Diabetes 10-Plex test system, Bio -Rad, USA). Genotyping for polymorphic markers of the PPARG gene (rs 1801282) was performed using PCR with allele-specific primers from Synthol. Amplification was carried out using a programmable thermal cycler Q5 (Bio-Rad). Statistical data processing was carried out using SPSS Statistics 26.0 software. To compare the frequencies of alleles and genotypes by a qualitative binary trait, the χ^2 test was used. To assess the associations of polymorphic gene variants with different phenotypes, odds ratio (OR) and 95% confidence interval. Statistically significant differences were considered at $P < 0.05$.
Results
Analyzing the distribution of frequencies of alleles and genotypes of the polymorphic marker of the PPARG gene (rs 1801282), no statistical significance was found in the group of patients with prediabetes and in the control group. Comparative analysis showed that homozygotes for the C allele significantly differed from the carriers of the minor allele G in higher levels of WC ($P < 0.001$), glycated hemoglobin ($P < 0.001$), glycemia 2 hours after glucose loading ($P < 0.05$), C-peptide ($P < 0.001$). Also, homozygous carriers for the major allele C were associated with the level of HbA1C≥5.7% ($P < 0.001$) and the level of systolic blood pressure above the target level ($P < 0.001$). There were no significant differences in HOMA-IR, HOMA1-β parameters, which is probably due to the small sample size included in the analysis.
Conclusions
Analysis of the polymorphic marker of the PPARG gene (rs 1801282) demonstrated the association of the major allele C with higher rates of carbohydrate metabolism and B-cell secretory activity, as well as cardiovascular risk factors, which makes it possible to use this parameter as a predictor of the development of early carbohydrate disorders.

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EP1100

Diabetes mellitus secondary to BRCA2 gene mutation: the importance of insulin resistance and genetics in dysglycemia

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Introduction
Diabetes *mellitus* (DM) results from a defect in insulin secretion and/or its action. The Breast-Cancer Susceptibility Gene 2 (BRCA2), like BRCA1, is a tumour suppressor gene, and its mutation is associated with an increased risk of breast cancer and, in males, testicular cancer. In patients with the BRCA1/2 mutation, the level of Insulin-like Growth Factor (IGF)-1 and, consequently, the peripheral sensitivity to insulin are reduced, suggesting that this could be the causal relationship between insulin resistance and the development of dysglycemia in these patients.
Clinical case
Male patient, 26 years old, with normal weight, referred to the Endocrinology consultation for DM of dubious etiology diagnosed in routine analyses with his attending physician (fasting blood glucose of 103 mg/dl and blood glucose 2h post-75g of oral glucose of 334 mg/dl). He reported polyuria and polydipsia of moderate intensity and of indeterminate evolution time, without associated weight loss. He had a diagnosis of testicular teratocarcinoma in 2012, aged 16, for which he undergone left orchiectomy, followed by chemotherapy with bleomycin, etoposide and cisplatin (between 2013 and 2014) and having the genetic study revealed mutation in the BRCA2 gene. He also has atopic eczema, currently medicated with dupilumab, without glucocorticoid therapy. He have a family history of DM in the maternal grandmother. Hypoglycemic therapy was started by his primary care physician with metformin 1000 mg/day, with subsequent referral to a tertiary treatment center. No stigmata of any endocrinopathy on physical examination, namely acanthosis nigricans, was noted. Analytically, in the first consultation, he presented an occasional measurement of glucose of 188 mg/dl, with C-peptide of 6.58 pg/ml and anterior pituitary function without alterations. Anti-pancreatic islet antibodies, anti-GAD65, anti-IA2 and anti-ZnT8 were negative. Next Generation Sequencing panel for monogenic DM did not reveal any pathogenic variant. It was then added, due to insulin resistance, pioglitazone 15 mg/day and the patient manifested an excellent glycemic control (HbA1c 5.7%, TIR 90%, TBR 4%, TAR 6% and CV 29.7%), maintaining follow-up in the Endocrinology consultation.
Conclusion
We report the case of a young, normal-weight patient with DM and mutation in the BRCA2 gene whose evaluation excluded autoimmune etiology and MODY diabetes, which highlights the clinical heterogeneity associated with dysglycemia. The possible relationship between insulin resistance and mutation in the BRCA2 gene could be the etiology of DM in this context, emphasizing the importance of assessing glucose metabolism in this population subgroup.

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EP1101

Köbberling disease: Familial Partial Lipodystrophy type 1 associated with thyroid cancer

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Introduction
Lipodystrophic syndromes are rare and heterogeneous disorders characterized by the complete or partial deficiency of adipose tissue. They can be classified according to the extent of fat loss in generalized or partial subtypes and genetic or acquired based on the pathogenic mechanisms.
Case report
A 37-year-old man was referred to our department with a history of nonalcoholic steatohepatitis associated with high levels of triglycerides (720 mg/dl) and structural alterations of anterior cervical region on computed tomography scan: right thyroid lobe irregular hypoechoic nodules with micro-calcifications and increased vascularity and multiple superior mediastinal and right sided cervical lymph nodes with necrosis and calcifications. On physical examination, the patient had a body mass index of 31.71 kg/m2 with a clear pattern of fat loss in the extremities (especially lower limbs), with truncal obesity and a slightly increased fat in the face and neck and acanthosis nigricans in the posterior cervical region. When questioned, the patient reported these physical changes for about 6 months with an unremarkable family history. Laboratory tests showed the following results: fasting serum glucose 80 mg/dl with HbA1c 4.9%, total cholesterol 151 mg/dl, high-density lipoprotein cholesterol 59 mg/dl, low-density lipoprotein cholesterol 81 mg/dl, triglycerides 70 mg/dl, normal alanine aminotransferase and aspartate aminotransferase, but with high gamma-glutamyl transferase 216 U/l and normal hormonal profile. HOMA-IR was 3 suggestive for insulin resistance. Thyroid ultrasound showed similar features like CT scan. Truncal subcutaneous adipose tissue with minimal edema was observed on ultrasound imaging alongside with pericardial and perivascular fat on echocardiography. A whole-body dual energy x-ray absorptiometry scan showed a fat mass index of 10.02 kg/m2 (class one obesity), with slightly elevated Trunk %fat-to-Legs %fat ratio of 1.2 and an increased Arms %fat-to-legs %fat ratio of 1.52, indicating an increased truncal and arms fat mass redistribution. The patient will be directed to the surgical department for total thyroidectomy.
Discussions
A clinical diagnosis of FPLD type 1 was made by the described findings. Although it appears that this syndrome is familial, it may also occur spontaneously and only a few affected women have been reported until now. The genetic defect associated with

Köbberling-type lipodystrophy is currently unknown, but latest research suggest that this form of lipodystrophy may have a polygenic etiology. Further management includes close monitoring and multidisciplinary approach regarding metabolic complications associated with this disorder.

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EP1102

Cystic fibrosis: diagnostic keys and new treatments

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A 47-year-old male with a history of severe persistent asthma and recurrent respiratory infections with admissions to the Pulmonology Department. The patient underwent a study due to weight loss, diarrhoea and Ca 19.9 elevation. Imaging tests (abdominal CT and MRI cholangio) were performed, which highlighted severe pancreatic fat infiltration. The cystic fibrosis study was completed with genetics (positive: two heterozygous switches F508del and D1152H), sweat test (45 mmol/l –> Intermediate, suggests possible CF) and pancreatic elastase in feces (<5.50 mg/g). Finally, the patient was diagnosed with cystic fibrosis, heterozygous for F508del and D1152H associated with exocrine pancreatic insufficiency. He was referred for follow-up in the Pulmonology and Endocrinology consultation to optimize treatment and follow-up, as well as to assess the start of new therapies. Patients diagnosed in adulthood have slightly impaired lung function and a low incidence of pancreatic involvement, so their prognosis tends to be favorable. On the basis of the foregoing, they will require less intensive treatment and often will not need digestive enzymes or nutritional supplements. An accurate diagnosis through imaging tests is essential for the correct management of this entity. In our case, it was the key clue, since the disease was not suspected by the patient's condition. With the advent of new modulator drugs (potentiators and correctors) of the CFTR protein, a very hopeful future opens up, since it radically changes the natural history of the disease. At present, the available pCFTR modulators are divided into potentiators, such as ivacaftor (IVA), which increases the probability of opening/activation of the chloride channel; and the correctors lumacaftor (LUM), tezacaftor (TEZ), and elexacaftor (ELX), which facilitate protein processing and transport to the cell membrane, increasing the amount of pCFTR on the cell surface. Currently, there are 4 pCFTR modulator drugs authorized by the European Medicines Agency (EMA): Kalydeco® (IVA) for over 4 months, Orkambi® (LUM/IVA) for over 2 years, Symkevi® (TEZ/IVA) for over 6 years and Kaftrio® (ELX/TEZ/IVA) for ages 6 and up; in the EU the last two in combination treatment with Kalydeco® (IVA). Each of the medications described is approved for specific CF patients and mutations, so not every approved modulating therapy is indicated for all of the CFTR genotypes. Our patient benefited from treatment with Kaftrio, an oral therapy approved for patients with at least one Phe508del mutation in the CFTR gene.

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EP1103

Tigecycline as a ausative agent of severe hypoglycemia

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Drug-induced hypoglycemia is a major clinical concern. Antibiotics are one of the causative agents to cause hypoglycemia. Tigecycline, which is a glycylcycline antibiotic, has a broad spectrum of activity, including activity against drug-resistant gram-positive and negative organisms. Ifs side effects are significant but hypoglycemia and severe hypoglycemia is a rare finding during treatments. Our aim is to present an event of severe hypoglycemia in a patient with type 2 diabetes mellitus with replacement renal therapy, hemodialysis after initiating tigecycline.

Case presentation

A 54 years old female diagnosed with tip 2 diabetes mellitus was under treatment with basal-bolus insulin-therapy and oral antihypertensive drugs. She started hemodialysis 24 months ago. She complained of recurrent fever since the last 7 months and was treated with several antibiotics. In two separated blood cultures patient resulted positive for methicillin-resistant *Staphylococcus epidermidis* (MRSE). Based on antibiogram, we started treatment with tigecycline 100 mg/day. After 6-8 hours from the first dose, patient complicated with events of hypoglycemia and then continues with of severe hypoglycemia (40-47 mg/dl). Laboratory investigations showed: hemoglobin level 10 g/dl; total WBCc 14.68×10^9/l (neutrophils 82%, lymphocytes 17%); platelet count 230 K/uL (150-400); blood urea 277.83 mg/dl (0-50); serum creatinine 12.0 mg/dl (0.57-1.11); serum sodium 140.00 mEq/l (136 – 148); potassium 6.6 mEq/l (3.7-5.5); calcium 9.14 mg/dl (8.4 - 10.2); HbA1c 6.5% and procalcitonin level was 2.01 ng/ml. The patient continued to have hypoglycemia for about 16-18 hours after the last dose. We didn't find any reasons to explain the cause of episodes of hypoglycemia. Her insulin-like growth factor (IGF-1) was normal at 206.0 nmol/l (49.6–204), C peptide levels was 1.82 ng/ml (< 5.19), cortisol levels was 724 nmol/l (68.2-327) and ACTH level was 25.70 pg/ml (7.2 - 63.3). Patient didn't have high level of insulin in the blood (insulin 4.11 mIU/l range 2.6-24.9).

Conclusions

We report a case of a diabetic patient with end stage renal disease on hemodialysis that experienced severe hypoglycemia episodes induced by tigecycline. To our knowledge, this is one of the limited case reports of sustained severe hypoglycemia due to tigecycline. Severe hypoglycemia is a serious event and immediate intervention is needed to correct it otherwise the outcome can be fatal.

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EP1104

Impact of COVID-19 pandemic on nationwide antidiabetic drug utilization

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Introduction

The COVID-19 pandemic resulted in various outcomes that have altered disease prevalence and drug utilization patterns. Our study aimed to evaluate the trends in the utilization and costs of antidiabetic medications before and during the COVID-19 outbreak in Turkey.

Methods

We obtained nationwide sales data for antidiabetics from IQVIA Turkey, spanning between April 2018 and March 2022. Mean monthly drug utilization and expenditure trends before the pandemic (April 2018-March 2020) and during the pandemic (April 2020-March 2022) were compared. Drug utilization was measured by defined daily dose/1000 inhabitants/day (DID) unit.

Results

Utilization of antidiabetic drugs increased significantly from 125.7 ± 12.5 DID before the pandemic to 158.3 ± 25.7 DID during the pandemic ($P < 0.001$). There was a considerable rise in the use of oral antidiabetics, with utilization increasing from 71.2 ± 6.9 DID prior to the pandemic to 90.6 ± 17.2 DID ($P < 0.001$). Moreover, insulins and their analogs were utilized more frequently during the pandemic, rising from the pre-pandemic levels of 52.4 ± 6.7 DID to 65.4 ± 10.0 DID ($P < 0.001$). Marked increases were observed in the expenses for antidiabetics, moving from 65.4 ± 8.4 to 86.7 ± 15.0 million Euros ($P < 0.001$). These increments were noted both for oral antidiabetics (from 35.8 ± 5.6 to 50.4 ± 10.2 million Euros, $P < 0.001$) and insulins (from 27.1 ± 3.7 to 33.4 ± 5.7 million Euros, $P < 0.001$).

Conclusion

Our study demonstrated a surge in the utilization and expenditure of antidiabetics in the two years of the COVID-19 pandemic in Turkey, compared to pre-pandemic levels. These results should be considered in evaluating the association of COVID-19 infection with chronic diseases such as diabetes, as well as the outcomes of interventions to facilitate access to drugs for extraordinary circumstances.

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EP1105

Rechallenge with a single-pill combination of sitagliptin plus extended-release metformin in patients labelled as metformin-intolerant: Mostly successful

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Introduction
Extended-release (ER) metformin has been available in many countries for the last two decades, and it may have definite advantages vs. conventional (i.e., immediate-release) metformin: Reportedly, it may reduce gastrointestinal adverse effects by about half, thus increasing compliance; moreover, the once-a-day schedule may contribute to increased adherence and persistence, and hopefully improved outcomes. However, ER metformin was unavailable in Spain until 2022: when generic sitagliptin became available, a single-pill combination containing 50 mg sitagliptin and 1000 mg ER metformin was released, while monocomponent ER metformin is still unavailable. We undertook to rechallenge metformin-intolerant T2DM patients treated with a DPP4 inhibitor with the sitagliptin plus ER metformin single-pill combination in order to assess its tolerability and efficacy.
Methods
T2DM patients with HbA1c $>7\%$ and GFR (CKD-EPI) >45 mL/min/1.73m^2, labelled as metformin-intolerant due to gastrointestinal symptoms, and treated with a DPP4 inhibitor (with or without additional hypoglycemic medication) were switched to the 50 mg sitagliptin plus 1000 mg ER metformin single-pill combination, taking 1 pill with the evening meal in the first month and afterwards 2 pills together if the tolerance was good. Additional medication, if any, was unchanged. Data on glycemic control were compared (paired t-test) between the baseline visit and a follow-up visit 3-4 months afterwards. Tolerance data were obtained by questionnaire in the follow-up visit. All patients included gave informed consent. Data are given as mean $\pm$ sd.
Results
38 patients were included, 24 (63%) were women, age 55 ± 8 years, diabetes duration 7 ± 3 years. 32 (84%) tolerated 1 pill, although 12 of them (32% of the total) had minor gastrointestinal symptoms which subsided along the first month and did not cause withdrawal. 27 (71%) of the patients tolerated 2 pills, although 7 of them (18% of the total) had minor symptoms after the dose increase. Fasting plasma glucose was reduced from 178 ± 38 mg/dl to 139 ± 26 mg/dl ($P < 0.001$) in those who tolerated 1 pill, and to 128 ± 19 ($P < 0.001$) in those who tolerated 2 pills. HbA1c was reduced from $8.2 \pm 1.1\%$ to $7.8 \pm 0.8\%$ ($P = 0.058$, 1 pill) and $7.6 \pm 0.7\%$ ($P = 0.015$, 2 pills). Of 11 patients who did not tolerate the rechallenge, 8 (21%) reported diarrhea, 4 (11%) flatulence, 2 (5%) abdominal pain, 2 (5%) nausea and 1 (3%) dyspepsia.
Conclusions
Rechallenge with ER metformin plus sitagliptin in patients intolerant to conventional metformin was mostly successful, with 5/6 tolerating 1 pill and 7/10 full dose. Side effects were minor, and glycemic control was improved.

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EP1106

Diabetes treatment with dapagliflozin and its combinations: Insights from clinical practice

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Background
Despite global guidelines recommending initiation of SGLT2i drugs like dapagliflozin in type 2 diabetes (T2DM) patients with cardiovascular (CV) or renal risk, its clinical translation is still lacking in India.
Objective
To understand clinicians' perspectives regarding the association of CV risk and T2DM in Indian patients, and the need for the use of combination therapies with dapagliflozin in T2DM patients, in Indian clinical practice.
Methods
A cross-sectional, questionnaire-based survey involving 873 diabetologists and consulting clinicians was conducted. The survey questionnaire consisted of 30 questions that accessed T2DM patient profiles and clinicians' preference for treatment approach, dapagliflozin use for cardiorenal protection and its combination therapy.
Results
In routine clinical practice, 73% of clinicians observed more than 20 T2DM patients weekly. The majority of these patients (91%) were aged between 40 – 60y. The clinicians observed that these patients presented with varying comorbid conditions like obesity (39%), coronary artery disease (38%) and chronic kidney disease (14%). 37% of clinicians said CV risk was observed in 50 – 80% of T2DM patients. In the treatment of T2DM patients, 44% of clinicians preferred SGLT2i, followed by DPP4i (31%) and SU (28%) as the first choice of antidiabetic class of drug other than metformin. Among the SGLT2i class, dapagliflozin (91%) was the most preferred choice. According to 55% of clinicians, the most prominent clinical benefit of dapagliflozin was a reduction in HF hospitalisation and 69% suggested dapagliflozin to be the most effective SGLT2i in patients with renal impairment. Around 94% of clinicians agreed that early initiation and aggressive intensification of combination therapy should be done and 58% preferred SGLT2i-based combinations. In the case of SGLT2i + DPP4i fixed-dose combinations (FDC) for T2DM patients with CV or renal risk, 79% of clinicians preferred dapagliflozin based FDC (66%: dapagliflozin+ sitagliptin and 13%: dapagliflozin + vildagliptin). In comparison, 76% strongly recommended the FDC for a triple combination of dapagliflozin + sitagliptin + metformin. All the clinicians agreed that SGLT2i drugs like dapagliflozin must be initiated in T2DM patients with comorbidities, and 98% opined that SGLT2i like dapagliflozin is one drug across HF spectrum among T2DM patients. However, 89% of clinicians were concerned with dapagliflozin underutilisation in Indian patients.
Conclusion
The findings from the survey highlight the clinical benefits of dapagliflozin and its FDCs in T2DM patients with CV/renal risk. Early initiation and aggressive intensification with dapagliflozin FDCs in T2DM patients is highly recommended.

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EP1107

HbA1c and Lipid Profile Indices: Useful for cardiovascular risk prediction in non-diabetics?

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Aims
Glycosylated hemoglobin (HbA1c) is a marker which demonstrates 3-month average level of blood glucose level. In individuals with high blood sugar level for a long time is associated with increased risk of cardiovascular disease (CVD). There is a need for simple and cost-effective markers to determine the risk of CVD in primary health care settings. In this study, we aimed to investigate the value of HbA1c for predicting cardiovascular risk in healthy non-diabetic individuals.
Method
151 healthy individuals who applied to the check-up unit of Acıbadem University Hospital during 2017-2018 period is included in this study. The individuals who has HbA1c level 5.7 and above, and with an estimated glomerular filtration rate below 90 ml/min were excluded.
Results
There was no statistical difference between the mean age, HbA1c and total cholesterol levels of 70 female and 81 male. Though, in male subjects, fasting blood glucose, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, uric acid, homocysteine, low-density lipoprotein (LDL), triglyceride, non-HDL values and total cholesterol/high-density lipoprotein (HDL), LDL/HDL, triglyceride/glucose ratios were found significantly higher compared to women. In the correlation analysis performed seperately among male and female patients, there was a significant positive correlation of HbA1c in males with total cholesterol/HDL and LDL/HDL ratios.
Conclusion
HbA1c value may contribute to the follow-up of non-diabetic patients in terms of cardiovascular disease risk. In the study of Yan Li *et al*., it was shown that an HbA1c level higher than 5.7% in non-diabetic patients with stent implantation due to coronary artery disease leads to an increase the risk of mortality. We have seen that lipid profile indices that can be used in addition to HDL and total cholesterol values which are used to determine the 10-year risk for CVD, show a significant positive correlation with A1c in young non-diabetic male individuals. We believe that even in

Table 1. Distribution of Biochemical Parameters by Gender

	Female (n=70)					Male (n=81)					
Gender	Mean Value	SD	Median Value	Minimum	Maximum	Mean Value	SD	Median	Minimum	Maximum	p value
Age (year)	43.542857	9.05	45.00	24.00	66.00	41.48	8.50	41.00	23.00	62.00	0.135
Glucose (mg/dl)	87.542857	7.25	87.00	66.00	109.00	92.51	8.32	92.00	72.00	121.00	**0.001**
HbA1c (%)	5.3042857	0.23	5.40	4.50	5.60	5.29	0.27	5.40	4.40	5.60	0.929
BUN (mg/dL)	11.369265	3.36	10.91	5.50	21.30	13.41	3.23	13.20	5.60	21.50	**0.001**
(mg/dL)	0.6225714	0.08	0.62	0.41	0.81	0.88	0.09	0.89	0.62	1.10	**0.001**
eGFR (mL/dk)	113.64314	10.77	112.27	90.18	139.08	107.88	9.47	107.21	91.51	130.42	**0.001**
ALT (U/L)	27.48	13.74	24.00	13.40	97.00	44.75	24.48	40.10	13.70	162.90	**0.001**
AST (U/L)	18.197101	5.05	17.00	11.00	39.60	26.72	18.78	23.00	13.00	167.30	**0.001**
TSH (mIU / L)	1.8944923	1.04	1.80	0.01	5.61	1.64	1.00	1.29	0.16	5.51	**0.022**
Uric Acid (mg/dL)	3.7138462	0.93	3.52	2.50	6.49	5.38	1.05	5.45	2.75	7.74	**0.001**
Homosistein (Mmol/L)	8.565	1.72	8.22	5.52	11.53	13.58	3.49	13.27	9.59	26.19	**0.001**
T.Cholesterol (mg/dL)	191.44286	40.07	189.00	121.00	302.00	193.84	37.71	190.00	127.00	303.00	0.672
HDL (mg/dL)	64.411765	14.61	65.00	37.00	118.00	46.48	12.77	44.00	30.00	105.00	**0.001**
LDL (mg/dL)	118.19118	32.25	112.50	69.00	222.00	129.76	30.03	126.00	73.00	205.00	**0.018**
TG (mg/dL)	73.057971	31.02	67.00	25.00	168.00	132.25	79.18	112.50	36.00	518.00	**0.001**
T.Chol/HDL	3.064029	0.68	3.04	1.69	5.79	4.40	1.21	4.15	1.84	6.88	**0.001**
LDL/HDL	1.9052708	0.58	1.87	0.61	4.21	2.95	0.95	2.68	0.80	5.00	**0.001**
nonHDL	127.58824	35.39	122.50	74.00	225.00	148.00	37.14	148.00	88.00	243.00	**0.001**
TG/Glucose	0.8379473	0.35	0.78	0.27	1.93	1.42	0.79	1.18	0.44	4.75	**0.001**

HgA1c:Glicosylated Hemoglobin; BUN: Blood Urea Nitrogen; eGFR: Estimated Glomerular Filtration Rate; ALT: Alanine Aminotransferase; AST:Aspartate Aminotransferase; TSH: Thyroid Stimulating Hormone; T.Cholesterol: Total Cholesterol; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; TG: Triglyceride; SD: Standart Deviation

Table 2. The Relationship of HbA1c with Lipid Indices

	Female (n=70)		Male (n=81)	
	r value	p value	r value	p value
Age (year)	**0.439**	**0.001**	**0.405**	**0.001**
Glucose (mg/dl)	**0.351**	**0.003**	0.176	0.116
BUN (mg/dL)	0.090	0.468	-0.150	0.213
Creatinine (mg/dL)	0.098	0.419	0.165	0.140
eGFR (mL/dk)	**-0.374**	**0.001**	**-0.344**	**0.002**
T.Cholesterol (mg/dL)	0.135	0.267	**0.429**	**0.001**
HDL (mg/dL)	-0.037	0.763	-0.014	0.909
LDL (mg/dL)	0.096	0.436	**0.417**	**0.001**
TG (mg/dL)	0.163	0.181	0.201	0.074
ALT (U/L)	**0.265**	**0.027**	-0.076	0.502
AST (U/L)	**0.258**	**0.033**	0.016	0.890
TSH (mIU / L)	0.006	0.960	-0.145	0.254
Uric Acid (mg/dL)	0.038	0.763	0.190	0.115
Homocystein (Mmol/L)	-0.382	0.220	-0.304	0.102
T.Chol/HDL	0.136	0.268	**0.309**	**0.008**
LDL/HDL	0.095	0.442	**0.274**	**0.022**
nonHDL	0.162	0.187	**0.438**	**0.001**
TG/Glucose	0.126	0.301	0.189	0.093

BUN: Blood Urea Nitrogen; eGFR: Estimated Glomeruler Filtration Rate; T.Cholesterol: Total Cholesterol; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; TG: Triglyceride; ALT: Alanine Aminotransferase; AST:Aspartate Aminotransferase; TSH:

the early stages of coronary artery disease, HbA1c can be used for cardiovascular risk assessment in non-diabetic patients.

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EP1108

Utility of nutritional ultrasound for body composition in patients affected by obesity and overweight. Utility of nutritional ultrasound for body composition in patients affected by obesity and overweight

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Background and aim

Dual energy X-ray absorptiometry (DXA) is considered the gold standard to evaluate BC, even if it requires the use of radiations, an expensive equipment and cannot be performed at the patient's bedside. Nutritional ultrasound (NU) evaluates BC through the assessment of muscle mass and the abdominal subcutaneous (superficial and deep-layer) and visceral adipose tissue. We aimed

at comparing the accuracy and reliability of this emerging tool with DXA in patients with overweight or I grade obesity.
Materials and methods
Patients attending the Complejo hospitalario Universitario Insular Materno-Infantil de Las Palmas de Gran Canaria (España) with a body mass index (BMI) between 25 and 34.9 kg/m^2 were enrolled. NU (Esaote Medica, high frequency 12 MHz probe) was performed at the level of the QRF (lower third of the leg) for the evaluation of subcutaneous adipose tissue (SAT) and QRF circumference(mm); abdominal ultrasound measured total superficial fat (abdSAT) deep fat and pre-peritoneal fat (PAT). BC by DXA (Hologic) included the following parameters: Fat mass (FM gr, %), Free fat mass, Trunk fat mass gr, %), Total lean mass (LM), trunk lean mass.
Results
114 patients (40 males) were included. BMI was 29.9 $\pm$ 2.8 kg/m^2 and mean age was 53.9 $\pm$ 9.9 years. FM was 35.7$\pm$7.3%, while trunk fat mass was 36.6 $\pm$6.7%. After adjustment for age and sex, leg SAT showed a significant correlation with FM gr (r= 0.42, $P<$ 0.001), FM % (r=0.45, $P<$ 0.001), trunk fat % (r=0.27, P0.004). QRF circumference had a significant association with LM (P=0.005), leg lean and trunk lean ($P<$ 0.05). AbdSAT, and PAT reported strong association with total fat and trunk fat apposition;in particular deep abdominal fat and trunk fat % (r=0.47, $P<$0.001). After stratification for gender, male reported a better correlation between QRF and trunk lean (r= 0.46, $P<$ 0.005) and between abdSAT and trunk fat %(r= 0.5, $P<$ 0.005), compared to females, which instead reported an higher correlation index between PAT and trunk fat(r=0.41, $P<$ 0.001).
Discussion and conclusions
NU demonstrated to reach good correlations with the gold standard technique for BC, with the advantage of no X-ray exposure and more feseability. QRF evaluation seems to be more predictive of lean mass in males, and abdSAT seems to be more accurate for visceral apposition. PAT was the better NU index for the visceral obesity in females. Studies with higher sample power are needed in order to validate extend the use of NU for BC in clinical settings.

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EP1109

Design and development of mobile application for type 2 diabetes 'Diabetes 2 Learn'

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Introduction
Worldwide, diabetes is a common metabolic disorder that creates many complications. Nowadays a mobile-based application could be included in the therapeutic approaches of self-management.
Aim
This study presents the development of a mobile application named 'Diabetes 2 Learn' for people with type 2 diabetes inside the Greek population.
Methods
Google Play and App Store were examined for their apps on diabetes and their capabilities. Extending the capabilities and features of such apps and adapting for the Greek population, a mobile app was created. Java programming language was used to create the app, which is uploaded to Google Play for Android Operating System (AOS), because of its popularity and efficiency.
Results
The 'Diabetes 2 Learn' app for type 2 diabetes can be downloaded from Google Play to mobile devices with AOS, which is widespread in smartphones. The users can read information about diabetes and its complications, diagnosis, and symptoms, as well as dietary recommendations regarding Mediterranean diet and physical activity. Furthermore, the app can record blood glucose measurements and offers mg/dl graph support. The users also have quiz options to evaluate their level of knowledge on diabetes.
Conclusions
This software application was created for people with type 2 diabetes to help them manage their care by monitoring blood glucose, checking their knowledge on diabetes and benefitting from the advantages of adhering to the Mediterranean diet. The app has also been included in a study protocol which is in progress in Greek public hospitals.

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EP1110

A case of Wernicke's encephalopathy after sleeve gastrectomy

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Introduction
Wernicke's encephalopathy, resulting from thiamine deficiency, is a rare but serious neurological complication of bariatric procedures. The diagnosis is still difficult since the classic clinical triad (confusion, ataxia and oculomotor abnormalities) and the typical radiological features (areas of hyperintensity in mammillary bodies, thalamus, periaqueductal and periventricular gray matter) are not always present. Also, thiamine blood tests are not broadly available to confirm the diagnosis. Only a few cases of Wernicke's encephalopathy after sleeve gastrectomy have been reported in literature, nonetheless subjects can be underdiagnosed and their cases underreported.
Case presentation
We present the case of a 20-year-old female patient who developed Wernicke's encephalopathy after sleeve gastrectomy for grade II obesity (BMI 36.3 kg/m2) with metabolic complications (dyslipidemia, nonalcoholic fatty liver disease). She presented to the Emergency Department two months after surgery showing confusion, gait ataxia and horizontal nystagmus. Persistent vomiting and lack of compliance to vitamin intake were reported. She had already lost 19 kg, from 105 to 86 kg (BMI 29.8 kg/m2). Cerebral MRI showed acute bilateral lesions in periaqueductal and periventricular regions. After excluding chronic alcohol use, a diagnosis of Wernicke's encephalopathy was made. Unfortunately, thiamine dosage was not available. Parenteral thiamine supplementation was immediately administered (500 mg IV every 8 hours for 10 days), obtaining a progressive resolution of altered mental status, motor ataxia and nystagmus. On the contrary, anterograde, retrograde and working memory impairment persisted, as confirmed by cognitive tests. She was discharged with oral thiamine supplementation (300 mg daily) and underwent long-term physical, cognitive and psychological rehabilitation. After a 2-years follow up, she is compliant to a balanced fractionated diet and vitamin supplementation. Her body weight progressively reduced to 65 kg (BMI 22.5 kg/m2) and no other nutritional deficiencies developed. A new cerebral MRI showed regression of the neuroradiological findings. However, a minimal memory impairment remained.
Conclusion
Wernicke's encephalopathy is a concrete possibility after sleeve gastrectomy and should always be suspected in patients with recurrent vomiting, poor nutritional intake and non-compliance to vitamin supplementation. Immediate and aggressive thiamine supplementation is mandatory to prevent patients from irreversible neurological impairment, even though full recovery is not always achieved. A multidisciplinary approach (surgeon, endocrinologist, neurologist, dietitian, psychologist, physiotherapist) is required for the long-term management of these patients.

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EP1111

Maternally inherited diabetes and deafness (MIDD): easy to detect?

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Introduction
Maternally inherited diabetes and deafness (MIDD) that is caused by a pathogenic variant in mitochondrial DNA (mtDNA) can cause different phenotypes based on percent heteroplasmy load, with higher mutation load corresponding with disease severity. The m.A3243G mutation causes either classic MELAS or MIDD that is a partial form. The condition is characterised by diabetes, hearing impairment and maculopathy but can have several other clinical manifestations. Early recognition is important so that management of associated conditions and screening of maternal relatives can be implemented.
Case report
Caucasian female was incidentally diagnosed with type 2 diabetes aged 24 years during a routine medical check-up. BMI was 27 kg/m^2 at the time of diagnosis. She underwent some examinations: blood test included autoimmunity and genetic

study for maturity-onset diabetes of the young (MODY) that were negative. C-peptide level: 2.87 ng/ml (1.1-4.4). Human leukocyte antigen (HLA) was positive for DR-4/DQ-8. Her diabetes was initially managed with lifestyle interventions, metformin and empagliflozin. Also has a medical history for hypertension, microalbuminuria, hypercholesterolaemia and bronchial asthma. She has hadn't other complications. 4 years after diagnosis had sensorineural hearing loss so we request a genetic testing and found a probably pathogenic variant m.3243A>G heteroplasmy mutation in the MT-TL1 gene who is envolved in MIDD and MELAS syndrome. She has strong maternal family history of diabetes but no deafness. Following this diagnosis, she was referred for retinal screening where pigmented retinal lesions were found. The neurological evaluation was normal. Other hormones test were normal too. At the time of this diagnosis (6 yr after the beginning) she had a worsening of her blood glucose levels and Insulin was introduced into her medication regimen. We also changed empaglifozine for sitagliptin and added Co-enzyme Q10 (CoQ10).

Discussion

Recognizing mitochondrial disease in a cohort of patients with diabetes is not a simple task. It is not surprising, therefore, that it is common for mitochondrial diabetes to be misdiagnosed, even in the presence of other features that may provide clues as to the underlying genetic disease. Deafness usually precedes diabetes onset by 6 yr (intervals ranging 0-16) but in our patient deafness started 4 years after the diagnosis of diabetes. HLA polymorphisms associated with type1 diabetes as well as autoantibodies have only been anecdotally reported in mitochondrial diabetes mellitus (mDM). Reported cases were positive for HLA-DQA1/DQB1, but in our case, the polymorphism affected was DR4/DQ8 that isn't described in the literature for mDM.

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EP1112

Metabolic Control and Perinatal Outcomes According to The Planning or Lack of Planning of The Pregnancy

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Objectives

To analyze the data of patients seen at the Diabetes and Pregnancy Unit, assessing the frequency of pregnancy planning and whether there are differences in the degree of metabolic control before and during pregnancy, as well as in perinatal outcomes with respect to those who do not plan. All women of childbearing age with Pregestational Diabetes Mellitus(PGDM) should receive preconception counseling to optimize glycemic control, since preconception control is associated with a reduced risk of fetal malformations and perinatal mortality. In addition, pre-existing complications and associated comorbidities should be assessed, as well as the possible use of potentially teratogenic drugs. Despite this, only a minority plan their gestation.

Materials and Methods

Retrospective observational study. Data from 72 patients seen in the Diabetes and Pregnancy Unit, between were collected and analyzed.

Outcomes

Data of 72 women of whom 86.1% were Caucasian, 6.9% Arab, 4.2% Oriental and 2.8% South American, with a mean age of 34.5+/-6.25 years. Regarding the type of PGDM, 64(88.9%) had type 1 DM and 8(11.1%) had type 2 DM, with a mean evolution of 16.34+/-8.56 years since diagnosis. Only 28(38.9%) performed a previous planning, having 26 green light by the Endocrinologist at the time of gestation.

Conclusions

In those patients who do not plan, the initial HbA1c is significantly higher than in those who do plan. An early and close follow-up in the Diabetes and Pregnancy Unit allows improving metabolic control, achieving no significant differences at the end of gestation. No significant differences were observed in terms of perinatal adverse events, however, serious complications such as intrauterine mortality, fetal distress and major malformations occurred in those who do not plan, even though they did not reach statistical significance.

The perinatal and metabolic control data are shown in the table.

N(72)	Planning pregnancy($n=28$)	No planning pregnancy($n=44$)	*P*
PGDM TYPE			
DM1	40.6%	59.4%	
DM2	25%	75%	
METABOLIC CONTROL			
HbA1c pre-pregnancy(%)	6.57+/-0.66	7.73+/-1.43	**<0.001**
HbA1c 1st trimester(%)	6.38+/-0.66	6.99+/-1.07	**0.005**
HbA1c 2nd trimester(%)	6.11+/-0.53	6.29+/-0.76	0.23
HbA1c 3rd trimester(%)	6.41+/-0.61	6.44+/-0.74	0.85
BMI 1st trimester(kg/m2)	27.31+/-6.07	24.91+/-5.77	0.131
BMI 2nd trimester(kg/m2)	29.38+/-8.12	26.85+/- 9.47	0.246
PREGNANCY AND PERINATAL OUTCOMES			
Type of delivery			0.418
Cesarean	25%	11.4%	
Spontaneous	32.1%	38.6%	
Induced	42.9%	47.7%	
Weeks of gestation	37.42+/-1.85	37.23+/-2.5	0.74
Weight(gr)	3572.18+/-648.3	3415,88+/-825.33	0.40
Fetal suffering	0%	6.8%	0.329
Major malformation	0%	2.3%	0.472
Birth trauma	0%	0%	0.558
Hypoglycemia	35.7%	25%	0.643
Respiratory distress	14.3%	13.7%	0.581
Mortality	0%	4.5%(intrauterine)	0.120

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EP1113

Does the prebiotic and probiotic supplementation influence eating behavior in patients with obesity?

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Introduction

Disordered eating attitudes and behaviors are common and persistent in patients with obesity. The objective of our work was to evaluate the effect of prebiotic and probiotic supplementation on eating behavior in addition to a weight loss program in an adult population with obesity.

Methods

This is an interventional study involving 45 obese patients consulting the obesity unit of the Institute of Nutrition of Tunis in 2022. Patients were divided into 3 groups matched for age, sex and BMI: diet alone (G1), prebiotics (G2) (30g of carob/d) and probiotics (G3) (1 tablet of Lactibiane/d). Eating behavior and eating disorder symptoms (number of meals/day, number of snacks/day, snacking, night eating, binge eating, bulimia nervosa episodes) were assessed at T0 and at one month after the intervention (T1). No patients took antibiotics during the intervention period and no patient stopped taking carob. The statistical level of significance was defined as $P< 0.05$.

Results

The mean age was 48.73 $\pm$7.7 years with a female predominance (93.3% of women). The number of meals per day did not change between T0 and T1 for the three groups. There was a significant decrease in the number of snacks per day between T0 and T1 only for the diet alone group ($P=0.03$). Snacking prevalence significantly decreased in the three groups between T0 and T1 (G1: $P< 0.001$; G2: P0.04; G3: $P< 0.001$). For binge eating prevalence, a significant decrease was noted in the diet alone group ($P=0.001$) and the probiotic group ($P=0.002$). We also noted a significant decrease in nocturnal eating between T0 and T1 in the three groups (G1: P0.04; G2: P0.01; G3: P0.04). Indeed, at T0, 29% of patients had nocturnal eating and at T1, none of them had any. The prevalence of bulimia nervosa episodes significantly decreased in the three groups (G1: P0.09; G2: $P<$ 0.001; G3: P0.001). For the comparison between groups: The three groups were similar for improvement of eating behavior/disorder.

Conclusion

The significant improvement in eating behavior/disorder was independent of symbiotic intake. Following a weight loss program with a multidisciplinary team including at least a nutritionist and a psychologist is a promising alternative for improving eating disorders.

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EP1114

Wernicke Encephalopathy Due To Bariatric Surgery: Recounting A Case Report

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Introduction
Wernicke Encephalopathy (WE) is an acute neurologic disorder caused by thiamine deficiency. It is characterized by the classic triad of encephalopathy, gait ataxia and oculomotor dysfunction. It occurs in the setting of poor nutrition caused by lack of dietary intake or malabsorption. Since both of them can happen in patients that underwent bariatric surgery it is of utmost importance to prevent, recognize and treat this severe complication.
Case Report
41-year-old female with obstructive sleep apnea, gallstone disease, gastro-esophageal reflux and class III obesity (IMC 41,9 kg/m^2) underwent bariatric surgery roux-en-y gastric bypass in 2018. Preoperative blood analyses showed a low vitamin D, folic acid and zinc and was supplement for these deficiencies. There were no postoperative complications. Three months after the surgery, the patient enter the emergency department with complaints of abdominal pain and vomiting with 1 month of evolution. Upper endoscopy was performed showing a patent anastomosis. She was discharged with prokinetics and liquid diet. One week later she returned to the emergency department with intractable vomiting, indifference, inactiveness, axial ataxia, multidirectional nystagmus and hyporeflexia. There were no motor deficits. No abnormalities were demonstrated in the brain CT and MRI and the lumbar puncture showed no alterations. Blood analysis were normal except for: folic acid 2.1 ng/ml [reference range (RR) 2.2-17.5], total proteins 0.27 g/l [RR $>$ 0.45] and thiamine 37 nmol/l [RR: 66-300]. Thiamine parenteral replacement was immediately initiated. The evolution was favourable and the patient was discharged after 2 weeks. She maintain a gait deficit with myopathy in the right thigh confirmed by electromyography and biopsy.
Conclusion
We present a patient that developed severe vomits after Roux-en-Y gastric bypass leading to a state of protein malnutrition and severe hypovitaminosis B1. She developed WE with motor deficit sequelae possibly in the context of a radiculoplexus neuropathy setting. It is important to identify vomits and prevent malnourishment after bariatric surgery since WE has a rapid onset and detrimental course. Vitamin and mineral supplementation after bariatric surgery will prevent this severe complication.

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EP1115

Type 2 diabetes mellitus, primary biliary cholangitis and type 2 autoimmune hepatitis - a rare association

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The hepatic autoimmune diseases are rarely associated with type 2 diabetes mellitus (T2DM). Instead, it's more often encountered in people with type 1 diabetes mellitus in the context of polyglandular autoimmune syndrome (PAS). A 64-years old female diagnosed with T2DM for 8 years, hypertension and dyslipidemia currently under treatment with Dapagliflozin/Metformin 50/1000 mg twice daily, presented for her periodic diabetes consult complaining of marked fatigability and asthenia. The lab exams revealed: thrombocytopenia (47x10^3/mm^3), hepatocytolysis (GOT=424.14U/l; GPT=371.11U/l), cholestasis, elevated ESR and CRP, a protein electrophoresis pattern with decreased albumin and elevated γ-globulin and A1c=6.76%. The viral etiology was excluded. The abdominal ultrasound displayed marked splenomegaly, portal hypertension, slightly dilation of the intrahepatic bile ducts and increased caudate lobe. Due to hepatic status, the statin treatment was stopped, a switch from Dapagliflozin/Metformin to Glipizide was made and the patient was referred for a gastroenterology consult. The immunological profile was consistent with positive anti-nuclear and intense positive anti-mitochondrial M2 and M2-3E antibodies sustaining the diagnosis of an overlap syndrome with primary biliary cholangitis (PBC) and type 2 autoimmune hepatitis. The immunosuppressive treatment with Azathioprine 150 mg/day was initiated alongside ursodeoxycholic acid, L-arginine and Silymarin which led to significant improvement in the symptoms and lab exams. A subsequent dermatological consult established also a diagnosis of scalp psoriasis. The glycemic control under Glipizide was good with A1c $<$7% until present. This case illustrated a rare association of an overlap syndrome consisting of type 2 AH and PBC in an old female with type 2 diabetes. Despite immunosuppressive treatment and the conversion from dual to Glipizide monotherapy, the patient maintained a good glycemic control, emphasizing the role of this sulfonylurea in the management of the type 2 diabetes and liver diseases.

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EP1116

Nondiabetic hypoglycemia: the role of psycho-neurological care in primary diagnosis

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Introduction
Decreased glycemia in patients without diabetes mellitus (nondiabetic hypoglycemias; NDH) is a manifestation of severe diseases from endocrinopathies to malignant tumors. The most specific symptom of NDH is association of attack with the intake of carbohydrate-containing food. Hypoglycemia is usually manifested by neurological and mental disorders, and therefore, patients initially seek medical help not from an endocrinologist, but from psychiatrists and neurologists.
Objectives
To analyze the outcomes of the choice of primary specialists for medical care in patients with NDH.
Methods
anamnesis analysis of 431 patients with NDH aged 18-93 years.
Results
In 37% of patients with NDH, the correct diagnosis is delayed, among them 63% of patients have been initially observed by psychiatrists/neurologists.
Conclusions
In a significant proportion of patients with NDH, the correct diagnosis is delayed, and most of these patients receive pathogenetically unreasonable treatment from psychiatrists/neurologists, which increases the risk of hypoglycemic coma. Thus, the alertness of doctors, especially psychiatrists/neurologists, regarding the timely detection of NDH is extremely important.

	Group		
	1	2	3
Initial seeking to a specialist	Endocrinologist	Psychiatrist/ neurologist	General doctor, gastroenterologist, etc.
n (%)	274 (63,6)	102 (23,7)	55 (12,8)
Duration (Me (min-max)) of disease before verification* of NDH, months	0,03 (0,03-80,00)	84,00 (1,00-420,00)	18,00 (0,03-180,00)
	$p_{1-2,3}<0,001$; $p_{2-3}<0,001$		
Frequency of NDH verification* at the first seeking	97%	1%	9%
Frequency of hypoglycemic comas before NDH verification*	0,4%	20,6%	5,5%
	$p_{1-2}<0,001$; $p_{2-3}=0,012$; $p_{1-3}=0,002$		

*or an assumption

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EP1117

Can probiotics improve weight loss in patients with obesity?

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Introduction
Probiotics are made of good live bacteria and/or yeasts that naturally live in human body which are essential for the proper functioning of the microbiota. The objective of our work was to evaluate the effect of probiotics intake on anthropometric parameters in addition to a weight loss program.

Methods
This is an interventional study involving 30 obese patients consulting the obesity unit of the Institute of Nutrition of Tunis during the period from May to August 2022. Patients were divided into 2 groups matched for age, sex and BMI: diet alone and probiotics (1 tablet of Lactibiane*/day). Anthropometric measures (weight, waist circumference, BMI), body composition, and muscle strength (using handgrip dynamometer) were assessed at T0 and at one month after the intervention (T1).
Results
The mean age was 42.3 ±5.7years with a female predominance (75% of women). For the diet alone group, there was a significant decrease in body weight (-2.5 kg, *P*0,001), BMI (-0.9 kg/m^2, *P*0.001) and waist circumference (-1.7 cm, *P*0.01) between T0 and T1. For the probiotic group, in addition to the significant decrease in weight (-1.7 kg, *P*0.02), BMI (-0.8 kg/m^2, *P*0.03) and waist circumference (-2.9 cm, *P*0.001), we have noticed a significant decrease in fat mass (-2.5 kg, $P < 0.001$) and percentage fat mass (-1.7%, $P < 0.001$), as well as a significant improvement in muscle strength (+1.7 kg, *P*0.004). Although the decrease in body fat and body fat percentage and the increase in muscle strength were significant in the probiotic group and not in the diet alone group, the difference between the two groups was not significant.
Conclusion
For anthropometric parameters, the probiotic group was not superior to the diet alone group.

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EP1118

Does probiotics consumption improve glycemic parameters in adults with obesity?

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Introduction
Alteration of gut microbiota leads to increased intestinal permeability, inflammation, and metabolic disorders. The aim of our study was to determine the effect of probiotic supplementation on glycemic parameters in addition to a weight loss program.
Methods
This is an interventional study including 30 obese patients consulting the obesity unit of the Institute of Nutrition in Tunis. The patients were divided into 2 groups matched for age, sex and BMI: diet alone and probiotics (1 tablet of Lactibiane*/day). Glycemic parameters (fasting blood glucose, HbA1c, fasting insulin levels and HOMA index= insulin resistance score) were assessed at T0 and at one month after the intervention (T1).
Results
The mean age was 42.3 ±5.7 years with sex ratio Male/Female =0.25. Diabetes was found in 6.7% of patients in the diet alone group and 13.3% of patients in the probiotic group (the difference between the two groups was not significant *P*0.3). There was no significant difference between the two groups for glycemic parameters at T0 (fasting blood glucose (FBG), HbA1c, fasting insulin levels and HOMA index). For the diet alone group, there was a significant decrease only in HbA1c between T0 and T1 ($P=0.03$). For the probiotic group, we found a significant decrease in all glycemic parameters: FBG ($P=0.03$), HbA1c ($P=0.03$), insulin levels ($P=0.009$) and insulin resistance score ($P=0.008$). A statistically significant difference between the diet alone group and the probiotic group was found only for the decrease in fasting blood glucose ($P=0.02$).
Conclusion
Probiotics are superior to diet alone in improving the glycemic profile. Thus, they therefore have their place in the therapeutic arsenal of pre-diabetes and diabetes in patients with obesity.

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EP1119

Factitious hypoglycemia: psychosocial characteristics of patients

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Introduction
Hypoglycemia is a decrease of glucose in blood, which can lead to coma and death. One of the causes of hypoglycemia in patients without diabetes mellitus (DM) is deliberate intake of hypoglycemic drugs (factitious hypoglycaemia, FH, Munchausen syndrome).
Objectives
To present the psychosocial characteristics of patients with FH.
Methods
Anamnesis analysis of 431 patients with hypoglycemia aged 18-93 years.
Results
FH was diagnosed in 15 (3,5%) patients: due to taking antidiabetic pills ($n=5$) or insulin administration ($n=10$); age 34 (min-max: 18-47) years; $n=13$ females (87%); $n=1$ with DM and $n=11$ (73%) had relatives with DM; $n=2$ were medical workers and $n=1$ had medical worker as a relative. $n=5$ had a hypoglycemic coma in anamnesis, of them $n=2$ repeatedly. $n=4$ underwent unreasonable invasive intervention on the pancreas. FH was combined with factitious DM ($n=4$) and with factitious hypercorticism ($n=1$). Diagnosis, according to ICD-10: [F40] $n=3$, [F45] $n=2$, [F44.8] $n=1$, [F07.0] $n=1$ and [F48.0] $n=1$. $n=7$ (47%) refused psychiatric examination. 87% of patients were unemployed. The possible causes of FH were: free temporary accommodation and meals in the hospital, avoiding compulsory military service and work, speeding up kidney transplantation. After presenting evidence of FH, none of the patients confirmed this fact, but did not try to prove the opposite.
Conclusions
The main features of patients with FH are: young age, women, lack of work, relatives with DM. All patients, examined by a psychiatrist, had various mental disorders.

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EP1120

Comparative study on the efficacy and safety of various regimens of glucocorticoid therapy in patients with COVID-19 and Diabetes Mellitus

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Purpose
To determine the effective and safe regimen of glucocorticoids administration in patients with COVID-19 and with or without DM.
Materials and methods
We examined 276 patients with covid-19 and polysegmental pneumonia with CT (1-4) in inpatient treatment with an oxygen support level of up to 15 liters per minute, all patients were discharged from the hospital. Patients were divided into 2 groups according to the therapy they received. The first group of patients was treated with glucocorticoids (dexamethasone) - observational group of 205 patients, men -114, women -91 and the second was control group of 71 patient without glucocorticoid therapy: men -42, women -29. The number of patients with and without diabetes was assessed in each of the group. The observational group was divided into 3 subgroups according to the regimen of glucocorticoid therapy: in 1 subgroup of 68 patients dexamethasone was administered intravenous (i/v) once a day (the dose was 8 to 32 mg); in 2 subgroup patients received dexamethasone i/v 2 times a day (in a total daily dose of up to 32 mg) - 70 patients ; and in 3 subgroup of 67 patients dexamethasone was administered intramuscularly once daily (dose not less than 0.1 mg per 1 kg of body weight). In each subgroup number of patients with DM was assessed. All groups received standard therapy for COVID-19.
Results
in the observational subgroup of patients with DM at the end of the study Inflammatory factor such as: leukocytes increased by 35-41%, depending on the subgroup; the neutrophil-lymphocyte index (NLI) decreased by 28-44%; CRP decreased by 78.9-88.2% (p-0.001). In the subgroup of patients without DM, leukocytes decreased by 23-28%, NLI did not change, CRP decreased by 75-82.5% (p-0.01). In the Control group: no significant difference was obtained in the parameters of leukocytes, NLI. CRP decreased significantly in patients with DM by 39.7%, and without DM by 56.5% (p-0.0001).
Conclusions
1) The optimal regimen of glucocorticoid therapy is a single-dose intravenous or intramuscular administration of dexamethasone not less than 0.1 mg per 1 kg of body weight. 2) A statistically reliable effective and safe dose for patients with diabetes mellitus is 12 mg, without diabetes mellitus 11-12 mg.

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EP1121

Vitamin D status in childhood obesity: prevalence and implications in a group of children from Romania

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Introduction
Obesity and vitamin D deficit are risk factors for inflammation, insulin resistance, hypertension and impeded bone mineralization and also cardiovascular disease. type 2 diabetes and osteoporosis. As globally both conditions reach pandemic levels and the level of vitamin D negatively correlates with obesity we studied this correlation and impact on a group of children suffering from obesity.
Materials and method
We conducted a retrospective ecologic correlational study on 71 children from the south of Romania, who attended our nutrition clinic from 2020-2021, with the age median = 12, median BMI = 27, median obesity degree 145%.
Results and conclusion
A deficit of vitamin D was found in 31 patients (43.66%), 38.02% with mild deficit and 5.63% severe deficit. The vitamin D deficit positively correlates with the obesity degree (t value = 30,45, $P < 0.00001$) and the percent of body fat (t value = 26.96, $P < 0.00001$) Vitamin D deficit is present in nearly half of the children from the group, with deficit levels that statistically positively correlate with the degree of obesity and percent of body fat. Obesity is associated with a resistance to vitamin D supplementation and a new guideline for the substitution of vitamin D in this population as doctors still prescribe doses as for normal weight children. Keywords: pediatric obesity, vitamin D, body fat, deficit.

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EP1122

Type 1 diabetes after 10 years of evolution : complications and metabolic profile

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Introduction
Type 1 diabetes (T1DM) is an autoimmune disease that commonly affects a young population. Its evolution can be characterized by a frequent occurrence of degenerative complications. Our aims were to study microangiopathic complications, lipid profile, and the presence of other autoimmune diseases in type 1 diabetic patients whose diabetes has been evolving for 10 years or more.
Method
This is a descriptive cross-sectional study including T1DM patients (with diabetes of 10 years or more), conducted in department A of the National Institute of Nutrition in Tunis during the year 2022.
Results
Our study included 67 T1DM patients, predominantly female (61.2%). The average age of our patients varied from 16 to 67 years with a mean of 35 ± 12 years. The mean duration of diabetes progression was 17.7 ± 7 years. Among our patients 20.9% had hypothyroidism and 9% had hyperthyroidism. Celiac disease was present in 6% of patients. Only one patient had adrenal insufficiency. Microangiopathic complications were dominated by diabetic retinopathy (50.2%), then diabetic nephropathy (31.3%) and diabetic neuropathy (22.4%). More than 2 thirds of patients (86.6%) had poorly controlled diabetes (HB1AC > 7%) with a mean HB1AC of 10 ± 2%. Hypertriglyceridemia was present in 19.4% with a mean triglyceride level of 1.29 mmol/l. The mean LDL cholesterol level was 1.05 ± 0.23g/l. low HDL cholesterol levels were noted in 31.3% with a mean HDL cholesterol level of 1.24 ± 0.31 mmol/l. A positive association was noted between low HDL cholesterol and diabetic retinopathy ($P = 0.025$). The decrease in HDL cholesterol was also positively associated with diabetic neuropathy ($P = 0.45$) and diabetic nephropathy ($P = 0.05$).
Conclusion
Degenerative complications are common after 10 years of T1DM progression, hence the need for early management to prevent or delay the onset of chronic complications of T1DM. A low HDL cholesterol level could be a risk factor for the development of these complications.

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EP1123

Trends in Prescription of Anti-Diabetic Drugs and Metabolic Control in Type 2 Diabetes: 2015/2016 vs. 2020/2021

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Introduction
The development of new pharmacological classes for type 2 diabetes (T2D) treatment with extra-glycaemic benefits has led to the update of the treatment algorithm, presenting new effective alternatives to patients' insulinization. The present study aims to evaluate the evolution of prescription and its impact in metabolic control of patients enrolled on an educational diabetes program of a tertiary hospital.
Objectives
To evaluate trends on anti-diabetic drugs' prescription and metabolic outcomes in patients with T2D, comparing the two biennia 2015/2016 and 2020/2021.
Methods
240 patients were evaluated, 118 in 2015/2016 and 122 in 2020/2021, with no significant differences in general population characterization. In 2020/2021, there was a significant increase in GLP1 agonists (+72,3%, $P < 0,001$), SGLT2 inhibitors (+66,3%, $P < 0,001$) and metformin's (+10,1%, P0,030) prescription, contrary to a decrease in the use of DPP4 inhibitors (-58,9%, $P < 0,001$), insulin (-12,0%, P0,049) and sulfonylureas (-8,5%, P0,022). Additionally, there was an increase in the use of non-insulin anti-diabetic drugs in triple combination ($P < 0,001$) and in the de-insulinization rate (+11,9%, $P < 0,040$). In what concerns metabolic control, we found a higher reduction in weight (-0,4 kg vs. -4,0 kg, $P < 0,001$) and BMI (-0,16 vs. -1,38, $P < 0,001$) in 2020/2021, with no significant differences between biennia regarding HbA1c and blood pressure variation.
Conclusions
In 2020/2021, there was an increase in GLP1 agonists, SGLT2 inhibitors and metformin's use, as well as an increase in de-insulinization rate. In addition, we found a higher reduction in weight and BMI of patients. The differences found demonstrate a growing use of drugs with extra-glycaemic benefits, which reflected in a higher weight loss and allowed the discontinuance of insulin on a significative percentage of patients.

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EP1124

Anemia in the elderly diabetic subject

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Introduction
Anemia is common in the elderly subject over 75 years of age. The pathophysiological mechanisms of anemia are identical to those of the younger subject and the etiological investigation is based on precise diagnostic trees.
Objective
The objective of our study is to determine the prevalence of anemia in diabetic subjects over 75 years of age and to determine the associated factors.
Methodology
This is a descriptive cross-sectional study conducted at the National Institute of Nutrition of Tunis (INNTA) in 62 diabetic patients over 75 years old hospitalized in department A during the period February-December 2022. For each patient we conducted a medical history taking,a clinical examination with a blood count.
Results
We collected 62 diabetic patients. The average age of the population was 73.23 ± 3.28 years. Sixty five percent of the patients were female. The average age of diabetes was 16.30 years $\pm$ 8. The frequency of oral disorders was 88.9%. The socioeconomic level was low in 49.2% of patients. The prevalence of anemia was 22.2% with a mean hemoglobin of 12.58 g/dl ± 1.81. A significant association was noted with sex (P:0.011). Moreover, polymedication and digestive disorders were not associated with the presence of anemia (P:0.074) and(P 0.335) respectively.
Conclusion
Anemia is often discovered by chance. It would be a marker of the health state of the elderly which justifies an early diagnosis with an adequate etiological investigation in order to avoid the repercussion on the life quality of the patients.

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EP1125

Uricemia and lipid profile in adult population with obesity

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Introduction
Hyperuricemia is associated with an increased risk of cardiovascular diseases. The aim of this study was to examine the relationship between lipid profile and blood uric acid levels in an adult population with obesity.
Methods
Retrospective study including 200 patients with obesity who consulted the Obesity Unit of the National Institute of Nutrition in Tunis in 2021. Data were collected from patients' medical records. The lipid profile includes low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG) and total cholesterol (TC). Hyperuricemia was defined as serum uric acid greater than 6 mg/dl (360 µmol/l).
Results
The average age was 47.21 ± 13.88 years with a sexe ratio M/F = 0.33. Mean BMI was 41.2 ± 7 kg/m2. Dyslipidemia was found in 55.6% of cases. Hyperuricemia was found in 30.3% of cases. HDL cholesterol was inversely correlated with uric acid levels (r = - 0.2, P0.005). However, there was no significant correlation between TC, LDL, TG and uric acid.
Conclusion
The results of our study showed a strong association between uric acid increase and lipid disorder in patients with obesity. The detection and treatment of these abnormalities will improve the cardiovascular prognosis of patients.

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EP1126

What is the Impact of Prebiotic Supplementation on Depression Symptoms in Patients with Obesity?

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Introduction
People with obesity are at risk of psychological complications such as anxiety and depression. The objective of this study was to assess the effect of prebiotic supplementation in addition to a weight loss program on depression symptoms in an adult population with obesity.
Methods
Interventional study involving 30 patients with obesity consulting the obesity unit of the National Institute of Nutrition in Tunis between May and August 2022. Patients were divided into 2 groups matched for age, sex and BMI: diet alone and prebiotics (30g carob/day). All patients were screened for anxiety symptoms using the HAD score (depression dimension). The questionnaire was administered at T0 and one month after the start of the diet (T1).
Results
The mean age was 40.3 ± 6.7 ± years with a female predominance (80% of women). There was a significant weight loss in each group (diet only group: -2.5 kg P0.001 and prebiotic group: -2.2 kg, P0.003). However, for the comparison between groups, there was no significant difference (P = 0.7). At T0, depression related symptoms were present in 93,3% of the patients in the diet alone group (33.3% doubtful symptoms and 60% certain symptoms) and for the prebiotic group, depression related symptoms were present in 80% of patients (26.7% doubtful and 53.3% certain). At T1, there was a significant improvement in the HAD-depression score for the diet alone group (mean difference = 2.5, P < 0,001) and for the prebiotic group (mean difference = 3.1, P0.01). There was no statistically significant difference between the two groups for the improvement of HAD-depression score between T0 and T1 (P = 0.3).
Conclusion
The prevalence of depression symptoms was high in our population with obesity. The improvement of the symptomatology expression was not related to prebiotic consumption. It's probably related to the weight loss itself.

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EP1127

All's well that ends well

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Introduction
Diabetes can involve the musculoskeletal system causing frozen shoulder, Dupuytren's contracture, diabetic sclerodactyly, trigger finger, muscle infarction, diabetic amyotrophy, idiopathic lumbosacral radiculoplexus neuropathy, necrotizing fasciitis and many other complications. A case is described, who despite having multiple acute and chronic sequelae of diabetes, was successfully managed and discharged.
Case Presentation
54yrs old obese, Saudi gentleman with multiple co-morbids(Type 2 DM ≥ 10yrs, Hypertension, Chronic kidney disease(3B,A3), Proliferative DM retinopathy(awaiting intra-vitreal injections) & Grade I diastolic dysfunction), Chronic normochromic normocytic anemia(GI endoscopy-upper)-chronic inactive gastritis,(lower)-single rectal polyp(tubular adenoma on histopathology), was readmitted under Medicine department on 15.01.2023 with left hip pain, radiating to the thigh, with restricted activity for 2 weeks prior to the presentation. Rest of the workup-normal. Past history of proximal lower-limb weakness, double incontinence(2yrs) & cataract surgery. No allergies or addictions. Unremarkable family history He was on regular ACE-inhibitor, Calcium channel blocker, thiazide, loop diuretic, Linagliptin, statin, iron, Metformin and Glargine-100. Systemic review-unremarkable. BP 185/85mmHg, Pulse 74/m, regular, T-36.8 C, RR 19/m, O<info>2</info>sat 94%(on 6ltrsO<info>2</info>). Weight 104 kgs. Pallor + Bilateral pitting pedal edema + +, JVP raised. M. skeletal (Left hip) Upper medial thigh tender, but without warmth or erythema. Reduced passive and active movements of hip. Other joints unremarkable. CVS-S1, S2 audible + ejection systolic murmur + Neurology-symmetrical wasting of hands & quadriceps + absent deep tendon reflexes in lower limbs, along with bilaterally reduced vibration & pin-prick sensations. Rest-normal. The patient was diagnosed to have MRI proven extensive myositis of left pelvis & proximal thigh with focal myonecrosis and infective iliopsoas bursitis. Besides there was suspicion of early osteomyelitis of left ischio-pubic ramus & milder right sided myositis(CRP413.9 mg/l. He also developed acute on chronic kidney injury [S.Creatinine 307umol/l(59-104), and acute myocardial demand ischemia(serial ECGs-mild ST-T changes, TroponinT1040 ng/l(≥ 100 clinically significant), CPK438u/l(39-308), Echo[new RWMA(inferior wall) + mild LV systolic dysfunction(EF45%)], Myocardial perfusion scan-myocardial infarction of distal inferior wall. Other significant labs. Hb% 6.9g/dl, MCV89.8fl, TLC 17.8 $x10^9$/l,88% PMNs, HbA1c7.7%, S.albumin24.3g/l. CT chest-bilateral lower lobe opacities + mild pleural effusion. No pulmonary embolism. NCV/EMG-sensorimotor axonal polyneuropathy. The patient was treated with Frusemide, packed RBCs, Albumin, Insulin, Oxygen & broad spectrum antibiotics. An US guided aspiration & C/S from left iliopsoas bursa revealed MRSA organism and was treated for both bursitis & Osteomyelitis. He improved with the given treatment and was discharged home on 09.02.23..
Conclusion
Our patient exemplifies the presence of four co-existing musculoskeletal problems in close neighbourhood i.e. myonecrosis, myositis, infected iliopsoas bursitis and osteomyelitis. Diabetes was the common denominator amongst them.

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EP1128

Neuroleptics, a source of blood sugar imbalance not to be underestimed

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Introduction
Today, atypical antipsychotics offer the advantage of less frequent extrapyramidal effects compared to conventional neuroleptics, but they are associated with weight gain and diabetes mellitus.
Observation
A 31-year-old patient with positive diabetic heredity, followed for schizophrenia on Levomepromazine and Olanzapine. Having revealed his diabetes mellitus by a diabetic cardinal syndrome. Blood glucose = 3g/l. Urine dipstick shows ketonuria at 2 crosses, confirming the diagnosis of diabetic ketosis. Ideal weight, BMI = 18 kg/m2 and TDT = 79 cm. The physical examination was unremarkable except for a psychomotor slowdown. The aetiological assessment of the decompensation was strictly negative. The HbA1C on HPLC standardized on DCCT was 20%, a level confirmed on a second sample.

Discussion
Usually, the HbA1C levels observed at the discovery of T1DM are modest. This is explained by the noisy mode of revelation of this disease. However, in this case, the level was unusual, raising the suspicion of antipsychotic-induced T1DM. Indeed, it has been shown that the prevalence of diabetes is 10% in people treated with antipsychotics, 2 to 3 times higher than in a general population matched for age(*).
Conclusion
Drug-induced or drug-aggravated diabetes is a fairly frequent situation in clinical practice, often requiring multidisciplinary management
(*): Drug-induced diabetes: four classes at the heart of our clinical practice.12-10-2022.

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EP1129

Adherence to antidiabetic treatment in Tunisian type 2 diabetic patients

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Introduction
Poor compliance in chronic diseases, including diabetes mellitus, is a major and frequent problem, with serious consequences on morbidity and mortality of diabetics.
Objective
The aim was to assess adherence to antidiabetic treatment and to determine the consequences of poor compliance.
Patients and methods
This was a descriptive cross-sectional study conducted in the National Institute of Nutrition. 200 type 2 diabetic patients hospitalized between May and September 2022 were included. For each patient, we conducted a thorough interview and a biological check-up.
Results
The average age of our population was 58.56 $\pm$ 8.9 years with a female predominance of 66%. The average age of diabetes was 13.16 $\pm$ 7.8 years with an average HbA1c of 10.28 $\pm$ 2% and fasting blood glucose of 12.13 $\pm$ 5.42 mmol/l. 1/5 of our population did not accept their diabetes. The majority of our patients were on Oral-Diabetic-Agents (ODA), 21% on insulin and 39% on ODA and insulin. Diabetes was complicated by retinopathy, nephropathy and neuropathy in 38.5%, 17% and 66.5% of cases respectively. 4/5 of our patients were adherent to the treatments. We noted a decrease in doses in 15% and omission of the usual doses in 22.5% of cases. There was a statistically significant relationship between adherence to treatment and acceptance of the diagnosis of diabetes ($P=0.03$), retinopathy ($P=0.009$) and HBA1C ($P=0.001$).
Conclusion
The lack of awareness of this problem leads to unnecessary intensification of antidiabetic treatment and may explain the large number of patients put on insulin.

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EP1130

Flash glucose monitoring in patients with DM3c

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Objective
Flash glucose monitoring (FGM) facilitates non-invasive glucose level assessment. Since November 2020 this system is subsidized in patients with type 3c diabetes (DM3c) Our objective was to describe the characteristics of these patients and their glycemic control expressed as times in range.
Methods and patients
Observational longitudinal clinical study between January 2021 and January 2023 in patients with DM3c.
Results
68 patients included. Mean age: 62.17 $\pm$ 10.43 years, with DM diagnosed with a mean age of 52.21 $\pm$ 13.02 years. 29.4% women. Mean BMI 25.33 $\pm$ 4.65 kg/m^2. 72.1% use of pancreatic enzymes in these patients. Total insulin dose 0.50 $\pm$ 0.32 UI/kg. 14.7% patients not using prandial insulin. DM3c etiology: 33.8% Chronic pancreatitis 61.8% Pancreatic surgery 4.4% Cystic fibrosis FGM metrics: A median use of 92.00% (with 85% use as 25th percentile). 10.26 $\pm$ 4.74% daily scans. 68.07 $\pm$ 19.57% time in range, 21.24 $\pm$ 11.34% time between 180-250 mg/dl, 8.47 $\pm$ 11.95% time above 250 mg/dl, 2.47 $\pm$ 1.00% time between 54-70 mg/dl, 0.28 $\pm$ 1.17% time below 54 mg/dl. Glycemic CV 32.89 $\pm$ 7.89%. 39.1%. GMI 7.07 $\pm$ 0.76%.
Conclusion
- The main cause of DM3c in our series was surgical pancreatic resection (61.8% of patients). Almost three quarters of them had also exocrine insufficiency.
- In our series of patients with DM3c, glycemic control was suboptimal due to hyperglycemia. Glycemic variation was adequate and hypoglycemia targets were met.

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EP1131

A 7.5 cm hyperdense heterogeneous incidental right adrenal mass: Is it cancer?

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Introduction
Although usually considered as benign tumors, cavernous hemangiomas are venous malformations due to endothelial dysmorphogenesis and not true neoplasias. They are usually asymptomatic but occasionally can cause compressive symptoms or serious internal bleeding. They may arise in almost any vascularised organ, but their presentation in an adrenal gland is highly infrequent, and can masquerade as pheochromocytoma, adrenal carcinoma or metastatic malignant lesion.
Methods
We performed a retrospective revision of the patient's clinical record and of the literature. The patient gave informed consent.
Results (clinical case)
A 72 year-old male, with obesity, type 2 diabetes and non-alcoholic fatty liver disease was referred to our Endocrinology clinic after the finding of a large right adrenal mass in an abdominal ultrasonography performed in the context of epigastralgia, dyspepsia and hepatomegaly. His office blood pressure was normal and he had no history of hyperkalemia or hypertensive episodes. There were no signs or symptoms suggesting Cushing's syndrome, no weight loss, skin lesions suggesting melanoma or other obvious signs of metastatic malignant disease. A CT abdominal scan and adrenal function tests were ordered. Plasma metanephrines (31/54 pg/ml), aldosterone, renin and aldosterone/renin ratio were normal, plasma cortisol after overnight suppression with dexamethasone 1 mg was also normal. The CT described a grossly spherical mass of 7.5 cm diameter occupying the right adrenal; the lesion was solid, hyperdense and heterogeneous, with multiple nodular and tubular foci. The presumptive diagnosis was adrenal carcinoma, distant metastasis, pheochromocytoma or hemangioma. The left adrenal gland showed a 1.6 cm hyperdense mass, not characterizable as adenoma. There were no other findings suggesting abdominal neoplasm or metastases. With functioning pheochromocytoma ruled out, the patient underwent laparotomy and right adrenalectomy which was uneventful; during the procedure a FNAC was obtained from the left adrenal. The pathology report was: Adrenal gland of 10.5 cm containing a 7.5 cm cavernous hemangioma, partially thrombotic, in the context of cortical adrenal hyperplasia or adenoma, negative for malignancy. The FNAC from the left adrenal was negative for malignancy also. The patient remains asymptomatic and 6 months after the surgery the adrenal function remains normal. For the follow-up of the left adrenal gland, an abdominal MRI scan has been ordered.
Conclusions
Adrenal hemangiomas are infrequent, but they should be included in the differential diagnosis of adrenal masses. They can masquerade as malignant lesions. Surgical treatment is often indicated in order to ascertain the diagnosis and to avoid complications.

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EP1132

Rare phenotype association between pulmonary NET and prolonged hyperkalemia after an unilateral adrenalectomy for primary hyperaldosteronism

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Introduction
We describe the case of a 68-year-old patient, having two MEN1-associated tumors that are not part of the classical triad, with a penetrance of only 40%, and 2%, according to the medical literature. Furthermore, she developed a persistent hyperkalemia after the unilateral adrenalectomy, which is rare and often missed.
Case report
In 2011, following a non-specific symptomatology (dry cough, fatigue), a bilobectomy was performed (medium and right inferior lobes), the patient being diagnosed with typical pulmonary carcinoid, as stated by the histopathology and immunohistochemistry tests. 9 years later, in May 2020, the patient was admitted to the ER for cardiac tamponade, the neoplastic etiology being revealed by the histopathological examination. Afterwards, the outcome of the immunohistochemistry assessment was fibrino-hematic pericarditis, with mesothelial reaction, without tumor aspects. A December 2020 octreoscan scintigraphy detected pericardial and hepatic lesions, indicating pulmonary carcinoid metastases. Therefore, 1 month later, octreotide treatment was initiated (Sandostatin LAR 30 mg/month). In July 2021, the patient undertook another octreoscan scintigraphy showing only a new L4 lesion. In November 2021, the laboratory findings pointed to primary hyperaldosteronism with a high ARR (>84.2 ng/dl per uU/ml), undetectable renin with PAC>20 ng/dl (42.1 ng/dl), and hypokalemia (2.9 mmol/l). The most recent unenhanced thoracic-abdominal-pelvic CT scan identified a 22mm adenoma in the right adrenal gland, which had been registered in the patient's medical records for 10 years. Due to endocrinological assessments which indicated subclinical hyperthyroidism, and a toxic multinodular goiter revealed by the thyroid scintigraphy, the Thyrozol treatment was restarted. In May 2022, the patient underwent right laparoscopic adrenalectomy. Gross pathologic examination revealed a 1.8 cm round, well-circumscribed nodule, while the microscopic examination confirmed the adrenal adenoma diagnosis. Pre-adrenalectomy, the patient's renal function was impaired, with a 32.3mL/min/1.73 m^2 eGFR. The postoperative PAC declined to a low level: 13.1 ng/dl, while the serum potassium levels surged to 7.43mEq/l, and the eGFR further decreased to 17.5mL/min/1.73 m^2 with cortisol levels within the normal range. Subsequently, fludrocortisone 0.1 mg daily was initiated, and the patient's potassium levels returned to the ULN (5.1 mmol/l) seven months after adrenalectomy.
Conclusion
Because of this rare phenotype association of primary hyperaldosteronism and pulmonary NET, the patient falls into both MEN1 and MEN4 syndrome. Close monitoring of postoperative potassium levels is crucial following adrenalectomy, especially those with altered renal function or advanced age, as they are at a higher risk of developing life-threatening hyperkalemia. Mineralocorticoid replacement therapy should be administered if necessary.

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EP1133

An audit of ten years experience of medullary thyroid carcinoma management from a tertiary care hospital of north India

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Introduction
Medullary thyroid carcinoma (MTC) is a rare thyroid malignancy originating from parafollicular C-cells. It accounts for 5% of all thyroid carcinomas.
Methods
A retrospective registry-based analysis of demography, clinical manifestation, genetics, management, and outcome of pathologically proven MTC cases presented in a tertiary care hospital in India was done.
Results
Among 71 evaluated cases, the mean age of presentation was 43.63 $\pm$ 11.41 years, and 62% were female. The median duration of symptoms was 23 months (IQR 12-34.75 months). The most common presenting complaint was goiter, present in 57 (80.3%) patients. Among the atypical presentation, one patient had ectopic Cushing's, one with hypertensive crisis in pregnancy due to pheochromocytoma, one patient had chondrosarcoma. Disease was detected incidentally in one patient who had prostatic carcinoma and underwent a PMSA scan, one had associated VHL. Median calcitonin and CEA level at presentation were 1566 pg/ml and 147.5 ng/ml respectively. Among the 25 RET protooncogene mutation assessments, 15 had the mutation positive. Twelve patients had MEN2A and 3 had MEN2B in this cohort one had Erβ positivity. Most of the patients were presented with stage 3 disease and an increasing trend of calcitonin level was observed as the stage of presentation advanced ($P=0.015$). Surgery was the primary modality of therapy offered in 95.8% of cases. The mean fall of calcitonin was 86.37 $\pm$ 36.11 percent, dependent on the tumor stage at presentation. Twenty-five patients received tyrosine kinase inhibitors as second-line or third-line therapy, 18 received sorafenib, and 10 and 5 patients received lenvatinib, and cabozantinib respectively according to availability. Two patients received PRRT with Lu 177. Thirteen patients had hand-foot syndrome,1 patient had membranoproliferative glomerulonephritis and one had bowel perforation as TKI adverse event. Median progression-free survival (PFS) time was 84 months. Patients with stable disease after the first modality had a PFS of 156 months compared to 72 months in those who had progressive disease at first follow-up (Chi-Square:5.244; $P=0.022$).
Discussion
An audit of 10 years of experience of MTC has been reported here. Some of the atypical presentation is documented. A tumour stage and its relation with baseline calcitonin, and responsiveness to TKI along with adverse events and determinants of PFS is also depicted. Hereditary MTC had an earlier age of onset. Limitation of the study being heterogenicity and truncation of data due to the retrospective nature of the study.

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EP1134

An interplay between primary hyperparathyroidism, Hashimoto thyroidis and thyroid cancer

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The incidence of well differentiated thyroid carcinoma (TC), mostly papillary, is higher among patients with primary hyperparathyroidism (PHPT) compared to the general population, despite the similar frequency of thyroid nodules. The link between TC and Hashimoto thyroiditis (HT) is attributed to chronic inflammation, but the molecular association is poorly undestood. Herein, we explore the possible interplay between HT, PHPT and papillary TC through a case report and a literature review. A 49-year-old female patient underwent right superior parathyroidectomy due to primary hyperparathyroidism and a total thyroidectomy because of a suspicious nodule. Histopathological findings were consisted of concomitant parathyroid adenoma and 2 mm papillary thyroid microcarcinoma with Hürthle cell features whereas the remaining tissue of the thyroid showed a typical pattern of HT. No capsular infiltration was detected neither the pathological lymph nodules. Postoperatively, TSH suppressive therapy was administered. Patient with PHPT should be closely monitored for the thyroid nodule on ultrasound, particularly if they have HT. The need of fine-needle aspiration (FNA) and cytological analysis of the suspected subcentimeter nodules in this setting is still to be clarified. Vice versa, when preparing for thyroidectomy, a serum calcium and parathyroid hormone should be measured. This preoperative screening can be a useful tool for detecting possible concomitant lesions and reducing reoperations and further complications.

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EP1135

Doege-Potter Syndrome, cause of paraneoplastic hypoglycaemia in a patient with a Solitary Fibrous Tumour: A Case Report

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Background
Non-islet-cell tumour hypoglycaemia (NICTH) is a rare paraneoplastic syndrome caused by an extra pancreatic tumour(1). Solitary fibrous tumour (SFT), amongst other tumours, is one of the rare causes of NICTH. We report a case of NICTH who presented with recurrent hypoglycaemias and was identified to have a fibrous tumour as part of the work up for his symptomatic hypoglycaemias.
Case Summary
A 75-year male had presented to the emergency department with severe symptomatic hypoglycaemia with a blood glucose of 0.9. His past medical history included hypertension and Gout. He was not on any medication that could have caused or contributed to a hypoglycaemia. His initial biochemical workup showed subnormal insulin and c peptide levels with low blood glucose reading (physiological response) in the presence of negative ketones and negative sulfonylurea screen. He also had a CT scan done as part of the workup for recurrent hypoglycaemia that showed a well-defined heterogeneously enhancing mass in the pelvis with no evidence of local or distant metastases. He was referred for surgery of his pelvis mass, the histology of which showed a SFT (immunohistochemistry positive for CD34 and STAT6, negative for S100, Sox10, CD117, DOG1, SMA and Desmin). Reassuringly, his symptoms of hypoglycaemias resolved completely post-surgery.
Conclusion
We present a case of NICTH secondary to SFT. The tumour secretes high molecular weight IGF-II(2) which has structural and biochemical homology with insulin resulting in hypoglycaemias(3). The management of NICTH is complete resection of the extra pancreatic tumour which eventually leads to resolution of the symptoms as happened in our case(4).
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EP1136

Parathyroid carcinoma - case report
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Parathyroid carcinoma (PC) is a rare endocrine tumor accounting for 0.5–6% or less in cases of primary hyperparathyroidism. According to The American Joint Committee on Cancer (AJCC) eighth edition, the histopathological criteria for PC include the presence of vascular invasion with capsular invasion and progression and/or metastasis to adjacent tissues. However, the small number of cases of PC makes it difficult to predict prognosis in the postoperative period of PC. We present two case report of PC: First, male patient, has chronic kidney disease in the dialysis stage and was monitored for PTH during his dialysis sessions. In September 2022 his PTH level was increase over 1911 pg/ml (15-65 pg/ml) and total calcium level corrected for albumin was 10.4 mg/dl. Because patient was also symptomatic (important bone pain), he was treated with total parathyroidectomy. Histopathological report was positive for right parathyroid carcinoma pT1NxL0V1Pn0 and Ki67 was positive in 5% of tumoral cells. Patient's calcium level decreased after the surgery needing high calcium doses and alfacalcidol. His PTH level decrease to 554 pg/ml and his calcium level normalize with orally calcium scheme. In order to detect secondary lesions, patient underwent whole body MIBI scintigraphy with no metastasis found on functional imaging. Second patient is a female patient diagnosed with a thyroid hipoechoic nodule in left thyroid lobe, with increased PTH level over 847 pg/ml and high calcium level of 13 mg/dl admitted for functional parathyroid imaging with MIBI. Scintigraphy report showed left superior parathyroid adenoma with dimensions about 1.5 cm. She was operated (October 2022) and the histopathological report was positive for parathyroid carcinoma in left superior parathyroid area pT2N0L0V0Pn0R1 with local invasion in adipose tissue and muscular strap, with Ki67 positive in 4% of tumoral cells. Her PTH level also decreased after the surgery at 112 pg/ml and she was referred for radiotherapy treatment. Functional imaging after the surgery (WBS MIBI scintigraphy) didn't found any distant secondary lesions. These case series of parathyroid carcinoma presents two different pictures: the initial diagnosis of secondary hyperparathyroidism vs primary hyperparathyroidism with no biological reason to think of parathyroid carcinoma vs many biological hints of parathyroid carcinoma, both successfully surgically treated, one with active monitoring and other with complementary radiotherapy treatment.
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EP1137

A diagnostic challenge: Is it metastatic papillary thyroid carcinoma or papillary thyroid carcinoma arising from intramedullar teratoma?
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Introduction
Papillary thyroid carcinoma (PTC) distant metastases without regional lymph node metastases are quite rare. Spinal cord teratomas are rare tumors mostly seen in children. To the best of our knowledge, the development of papillary carcinoma in intradural teratomas is theoretically possible, but has not been reported in literature.
Case report
A 36-year-old female patient admitted with the complaint of drop foot. On MRI, 20x11x20.5 mm lesion was observed at the T5 level and caused significant compression on the spinal cord. Surgical excision was performed due to drop foot. During surgery, a mass was detected on both sides of the spinal cord, the same color as the neural tissue and adherent to the cord, with a firmer consistency. Histopathological and immunohistochemical findings primarily suggested PTC metastasis. However, the presence of adipose tissue observed in the glial tissue neighborhood and the different degrees of immunoreactivity of the described glandular structures in different areas also consistent with a PTC on the basis of teratoma. With S100, glial tissue and adipocytes were positive. PAX8 and CK19 were positive in large areas. TTFI, HBME1, Galectin3, Gata3, ER, PR and EMA were positive in varying degrees and localizations. Thyroglobulin was positive in the secretions of the gland lumens. CEA, GCDP 15 and NapsinA were focal positive. In the thyroid gland no lesion or pathological FDG uptake could be detected via PET-CT. No pathological FDG uptake was observed in the neck. Also, 17x11 mm sized lesion at the lateral of the left ovary and anterior of psoas muscle had 3.5 SUVmax was reported. However this lesion was not seen in MRI evaluation. AntiTPO and antiTg were positive. In the thyroid ultrasonography, the parenchyma was heterogeneous and contained pseudonodular areas. A 4x4x6 mm well-circumscribed isoechoic solid nodule and a 6x7x8 mm isoechoic mixed solid nodule with cystic areas was observed in the left lobe. Thyroid FNAB performed from the index nodüle. The result was reported as atypia of undetermined significance. Total thyroidectomy followed by RAI ablation was planned as the treatment protocol to facilitate long-term follow up.
Conclusion
Clarification of the diagnosis of the neoplasms is imperative. Because treatment and follow-up protocols are shaped according to diagnosis. However, in some cases, the etiologic diagnosis of a neoplasm can be a real challenge for clinicians. As in our case, in unusual localized neoplasms, follow-up and treatment should be arranged by using additional diagnostic methods.
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EP1138

Clinical spectrum of ectopic Cushing's syndrome secondary to pheochromocytoma: A diagnostic and therapeutic challenge
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Introduction
The clinical presentation of ectopic Cushing's syndrome secondary to pheochromocytoma differs from the classic manifestations of these

endocrinopathies separately. This cosecretion causes greater morbidity, requiring a complex preoperative preparation. We describe two clinical cases, a 46-year-old male with grade II overweight and a 65-year-old female with grade I obesity, both with a personal history of hypertension poorly controlled with 7 and 3 antihypertensive drugs respectively and new-onset diabetes, the first as hyperosmolar hyperglycemic state, classified as type 2 diabetes mellitus (DM) treated with non-insulin hypoglycemic agents and insulin with progressive worsening of glycemic control despite a weight loss of 27.3% and 16.5% in the last 3 months respectively. The first case was associated with axonal sensory polyneuropathy in the lower limbs with clinical suspicion of Guillain-Barré Syndrome under follow-up by Neurology, while the second case reported paroxysmal tachycardia. On physical examination both had lower limbs edema and muscular atrophy in the extremities, but without cushing phenotype. Blood tests from the first and second cases reported: glucose 161 mg/dl and 284 mg/dl (70-100), potassium 2.2mEq/l and 2.3mEq/l (3.5-5.5), HbA1c 8.2% and 8.6% (<6.5%), pH 7.52 and 7. 48 (7.35-7.45), bicarbonate 46mmol/l and 33mmol/l (22-29), urine cortisol 9582 mgg/24h and >11253mg/24h (0.1-180), Nugent's test >75 mg/dl in both cases, ACTH 260pg/ml and 241pg/Ml (5-50), androgens, aldosterone, renin and normal ratios, metanephrine 2205 mg/24h and 1113 mg/24h (20-302), normetanephrine 1230 mgg/24h and normal (30-527) and methoxytyramine 1212 mg/24h and normal (103-434), respectively. Pituitary MRI was normal in both. In the first case, the thoraco-abdominal CT revealed multiple chronic dorso-lumbar vertebral fractures and left adrenal mass of 37 x 37mm compatible with pheochromocytoma, while the second case presented bilateral adrenal hypertrophy with right adrenal mass of 31 x 26mm compatible with pheochromocytoma. Given the clinical diagnosis of ectopic Cushing's syndrome due to pheochromocytoma, unilateral adrenalectomy was decided after being treatment with fenoxybenzamine and doxazosin, respectively, and metyrapone in both cases. Patology reported pheochromocytoma with free resection borders, PASS score 9 and 2 respectively, with ACTH expression. Both developed post-surgical primary adrenal insufficiency. Currently, both present normo-cortisolims ascertained with Synacthen test and remission of DM. Blood pressure controlled with 3 hypotensors and none, respectively.

Conclusions

In our experience, ectopic ACTH-producing pheochromocytomas are characterized by the association of uncontrolled hypertension, hyperglycemia, metabolic alkalosis and severe hypokalemia. In these scenarios, pre-surgical preparation with steroidogenesis inhibitors to maintain homeostasis is just as much a priority as alpha-adrenergic blockade.

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EP1139

Metachronous Double Pituitary Adenomas: Presentation of A Case and Literature Analysis

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Introduction

Prolactinoma is the most frequent secreting pituitary tumor. They are usually treated with dopamine agonists (DA) (bromocriptine and cabergoline), which are very effective in most cases. DA resistance consists of the impossibility of reaching normal prolactin levels and/or reduction of the adenoma by at least 50%.

Case presentation

We present the case of a 57-year-old man affected by visual disturbances and hypopituitarism (2019). Pituitary MRI showed a 25×30×27mm pituitary cystic macroadenoma with displacement of the pituitary stalk, suprasellar extension displacing and compressing the optic chiasm (superior temporal quadrantanopia) and lateral expansion towards the cavernous sinuses. The prolactin level was very high (345 mg/dl [3.7-19.4]), starting therapy with dopamine agonists and subsequent transsphenoidal surgical treatment (subtotal resection), with an anatomopathological diagnosis of prolactinoma. Subsequently, prolactin levels returned to normal (8.48 mg/dl) and the follow-up pituitary MRI revealed a marked reduction in the size of the pituitary tumor (9×9×8mm). Visual acuity improved remarkably, as did the symptoms of concomitant hypopituitarism. A new control MRI (2021) showed persistence and progression (17×19×15mm) of the adenoma, with new compression of the optic chiasm despite continued treatment with DA, maintaining, however, prolactin levels within normal limits (13.2 mg/dl). The patient underwent surgery again by endoscopic transsphenoidal resection. The histological study showed, on this occasion, immunostaining positive for gonadotropins (LH and FSH), but negative for HGH, ACTH, TSH, and prolactin. These findings allow us to provide an explanation for the lack of response to treatment in DAs.

Conclusion and discussion

Our results would confirm the diagnosis of a metachronous macroprolactinoma with a gonadotropin-producing macroadenoma. Infrequent association (60 cases described to date), whose etiopathogenic basis would lie in the appearance of two adenohypophyseal or intraadenomatous monoclonal expansions.

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EP1140

Cushing's disease: a rare case of long-term pasireotide therapy

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Background

Cushing's disease, the most common cause of endogenous Cushing's syndrome, is caused by a pituitary tumor secreting adrenocorticotropic hormone (ACTH). Careful selection of treatment and management of the disease and associated comorbidities are necessary to improve prognosis.

Case Presentation

A 32-year-old patient came to our observation for appearance of weight gain with abdominal obesity, hirsutism and amenorrhea. On suspicion of Cushing's syndrome she performed ACTH assay, cortisol h24 assay, cortisol after overnight DEX 1, Liddle's test with no cortisol suppression, UFC suggestive of ACTH-dependent Cushing's syndrome. The patient performed a pituitary MRI negative for pituitary adenoma. She then underwent selective lower petrous sinus catheterization with CRH test suggestive of Cushing's disease without lateralization. An exploratory transsphenoidal neurosurgical surgery was performed with removal of small pituitary lesion with erosion of the dura mater. The histological examination documented an ACTH-secreting pituitary adenoma. Ki-67 1%. Postoperatively, the patient reported well-being, with periodic checkups documenting disease remission. After two years, the patient presented again with symptomatology suggestive of Cushing's syndrome with appearance of biochemical recurrence of disease and pituitary MRI finding of post-surgical empty sella. Therefore, therapy with Pasireotide at a dosage of 0.6 mg subcutaneously at 2000 h. and 0.3 mg subcutaneously at 2000 h. was started. After initiation of therapy, the patient developed diabetes mellitus so hypoglycemic therapy were undertaken. In addition, pasireotide therapy was reduced to 0.3 mg twice daily based on blood and urinary cortisol dosage. The patient currently presents with target values of glycated hemoglobin and an initial hypocorticosurrenalism for which pasirotide therapy has been reduced and hydrocortisone therapy has been initiated.

Conclusions

Surgical resection of pituitary adenoma is the first-line treatment for Cushing's disease. However, surgery is not always successful, and disease recurrence may occur years after initial remission. Repeat transsphenoidal surgery can be considered in patients with biochemical evidence of recurrent Cushing's disease with visible tumour on MRI. Medical therapy becomes the therapy of choice in patients for whom there is no surgical target. Pasireotide is a multireceptor-targeted, second-generation somatostatin analogue with highest affinity for somatostatin receptor subtype 5 wich are expressed in corticotropinomas. The safety profile of pasireotide is similar to that of conventional somatostatin analogs, but with a higher frequency and degree of hyperglycemia. This is because pancreatic β-cells express SSTR5, which in turn regulates insulin secretion. Glucose and HbA1C levels increase immediately after the initiation of pasireotide treatment, necessitating hypoglycemic therapy.

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EP1141

Participation of pituitary activins in the control of prolactin during early post-natal development. Sex differences

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Serum prolactin levels increase progressively from birth to adulthood in female and male rats, being higher in females from birth. Although this gradual increase was associated with concomitant maturation of prolactin-releasing and -inhibiting factors, these processes do not fully explain some sex differences observed. In

in vitro studies, using lactotrophs in culture, from rats of different ages, in the absence of hypothalamic control, it was shown that the secretion of prolactin to the medium increases with age during the first weeks of life. These data suggest the involvement of intrapituitary factors. In the present work, the participation of pituitary activins, as paracrine factors, in the regulation of prolactin secretion during postnatal development was studied. Sex differences in this mechanism were also evaluated. Male and female Sprague Dawley rats aged 11, 23 and 45 days were used. Pituitary gene expression of activin subunits (*Inhba* and *Inhbb*) and activin receptors (*ActRI, ActRIIA and ACTRIIB*) was evaluated by RTqPCR. On day 11, female pituitary showed the highest expression of *Inhba* and *Inhbb*, being even significantly higher than that observed in males. The gene expression of activin subunits decreases with age in females, and the sexual differences disappears at 23 days. In contrast, the expression of *Inhbb* increases strongly at 45 days only in the pituitary glands of males, being the predominant activin subunit in this sex in adulthood. Gene expression of activin receptors (*ActRIB*, *ActRIIA*, and *ACTRIIB*) also decreases in females during postnatal development, while remaining relatively stable in males. We also evaluated the protein expression of *ActRIB* and its co-location with PRL. The proportion of lactotrophs (PRL+) expressing the receptor (ActRIB+) is highest in the pituitary glands of 11-day-old females and decreases with age. Activins have been described to inhibit PRL synthesis by inhibiting the transcription factor Pit-1 (or Pou1f1). This action not only involves the canonical pSMAD pathway, but also the phosphorylation of p38MAPK. At p11 almost all lactotrophs express p-p38MAPK in females, and its expression decreases with age with a concomitant increase in Pit-1. Our findings suggest that: the inhibitory regulation of pituitary activins on prolactin secretion is sex-specific; this regulation is more relevant in females during the first week of life and decreases with age; this intra-pituitary regulation is involved in the sex-differences observed in serum prolactin levels during postnatal development.

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EP1142

The underneaths of the pituitary stalk

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We are presenting a 23-year-old girl with a medical history of juvenile rheumatoid polyarthritis treated with methotrexate, that first addressed to the Endocrinology Department in may 2022 for primary amenorrhoea with poorly developed secondary sexual characters: height 160 cm, weight 48 kg, BMI 18.35 kg/m2, Tanner stages P1, B3. She was treated with oral contraceptives by the gynaecologist in the past without a hormonal assessment. The lab work revealed hypogonadotropic hypogonadism with a positive response to Triptoreline, low androgen hormones, persistent low IGF1, persistent, well-tolerated hypernatremia, and no inflammatory syndrome. A GH deficiency was excluded by glucagon test - GH peaks to 9.16ng/ml. Regarding the persistent hypernatremia with values around 151mmol/l, low copeptin, high normal renin (129.8uUI/ml) and normal aldosterone level, increased serum osmolality and decreased urinary osmolality, with the absence of increased thirst, the suspicion of adipsic diabetes insipidus was raised. It was initiated treatment with desmopressin with the improvement of sodium levels and serum osmolality in the first weeks, following a recurrence of hypernatremia afterwards. The treatment with desmopressin was suspended. Genetic testing was performed for a series of genes for pituitary insufficiency and other defects of steroidogenesis with the identification of a deficiency of 5 alpha-reductase (heterozygous SRD5A1 gene). The magnetic resonance imaging of the hypothalamic-pituitary axis revealed a pituitary microadenoma of 6.7/6/4.5mm. The presence of hypernatremia with low copeptin, persistent low IGF1 with positive stimulation of GH, and the hypothalamic origin of the amenorrhea raise the suspicion of pituitary stalk lesion. We cannot exclude a link between chronic inflammation during childhood because of rheumatoid polyarthritis or the methotrexate treatment and the hypothalamic-pituitary axis involvement.

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EP1143

Esthesioneuroblastoma As a Cause of Panhypopituitarism: Literature Analysis and Description of An Rare Case

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Introduction
Esthesioneuroblastoma (ENB), also known as olfactory neuroblastoma, is a malignant neuroendocrine tumor of the nasal fossa that arises from neurosensory receptor cells of the olfactory epithelium. It represents 3% of all nasal tumors. It presents a slow and progressive evolution that primarily affects the upper nasal mucosa and cribriform plate, with subsequent extension to the entire cavity and paranasal sinuses and can invade the orbit and cranial base.
Objective
We present the first case described in the literature of ENB with intracranial invasion as a cause of panhypopituitarism.
Case report
A 64-year-old man was assessed for bilateral hearing loss secondary to recurrent otitis, bilateral nasal respiratory failure (without associated epistaxis), holocranial headache, and sensation of stuffiness with Valsalva maneuvers. In the imaging tests (nasofibroscopy and CT of the paranasal sinuses) asymmetry was observed in the cavum, as well as a 35x30x30mm solid mass originating from the left sphenoid sinus, expansive, remodeling and rupturing the posterior wall of the sinus, clivus and sella turcica (invading the suprasellar region), affecting the pituitary stalk, with partial invasion of the cavernous sinuses, all suggestive of neoplasia of the sphenoid sinus. The laboratory study showed moderate hyponatremia, severe hyperprolactinemia (derived from compression of the pituitary stalk), central hypothyroidism, GH deficiency, and hypogonadism. The lesion was biopsied under general anesthesia (subsequently surgically removed by joint ear, nose, and throat intervention) with an anatomopathological diagnosis indicative of olfactory neuroblastoma. He required complementary radiotherapy treatment (64Gy).
Conclusion and discussion
As a neuroendocrine tumor, there are descriptions of paraneoplastic ectopic secretion of ACTH and Vasopressin in relation to olfactory neuroblastoma. No case of panhypopituitarism related to parasellar invasion of the pituitary stalk by this neoplasia has been described to date. Early diagnosis and treatment are necessary to achieve a favorable result, requiring close multidisciplinary collaboration.

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EP1144

Ectopic ACTH Syndrome in a Patient with ACTH-secreting Pancreatic Neuroendocrine Neoplasm and Focal Pituitary Lesion-Diagnostic Challenges

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Introduction
Pancreatic neuroendocrine neoplasms (Pan-NENs) account for 1-2% of all pancreatic tumors. Adrenocorticotropic hormone (ACTH)-producing PanNEN is an extremely rare neuroendocrine tumor that accounts for approximately 4-16% of ectopic ACTH-dependent Cushing's syndrome.
Clinical case
A 58-year-old female with arterial hypertension and type 2 diabetes was referred to the Endocrinology Department due to abdominal pain, muscle weakness, and unintentional weight gain. The hormonal evaluation confirmed ACTH-dependent hypercortisolemia: serum cortisol at 2000 h. 29.65 μg/dl, midnight serum cortisol 30.89 μg/dl, ACTH 87.6 pg/ml, UFC: 388.5 μg/24h, serum cortisol after 1 mg of dexamethasone: 22.71 μg/dl. MRI visualized a lesion measuring 8x5 mm and infiltrating the right cavernous sinus. Both the CRH stimulation test and high-dose dexamethasone suppression test were negative, whereas the combined dexamethasone-desmopressin test was positive. Given the inconclusive results, diagnostic imaging of the chest and abdomen was performed but revealed no signs of a tumor. Due to the presence of a focal lesion in the pituitary region, exploration of the sella turcica was undertaken; however, the lesion was beyond resectability. For this reason, pharmacological treatment was started. Inferior petrosal sinus sampling was performed twice, with inconclusive results. Pharmacological treatment of hypercortisolemia (pasireotide s.c., ketoconazole, cabergoline) was introduced. The patient remained in follow-up, lasting about ten years, despite pharmacotherapy, the features of ACTH-dependent hypercortisolemia persisted, and finally, in 2022, a full-body CT, visualized a focal lesion measuring 15x14mm in the pancreas tail. SPECT-CT somatostatin-receptor scintigraphy and Ga-68-HA-DOTATATE PET-CT did not reveal increased tracer accumulation and proliferative process features with high expression of somatostatin receptors. 18F-FDG PET/CT showed no proliferative

hypermetabolic changes. The patient underwent endoscopic ultrasound with tumor biopsy, and histological examination identified neuroendocrine cells with positive ACTH, CD 56, and chromogranin staining. Since the patient did not consent to surgery, treatment with lanreotide autogel 120 mg was introduced, which led to the normalization of hypercortisolemia. The dimensions of the pancreatic lesion remained stable. After the patient's consent, one year later, a tail resection of the pancreas was performed, resulting in complete normalization of the pituitary-adrenal axis.
Conclusions
The case described shows that extensive diagnostics and patient compliance are crucial in managing Pan-NENs. Ectopic ACTH production syndrome can be caused by very small focal lesions, so diagnostics of their location may last many years. Somatostatin analogs may be a treatment of choice in preparation for surgical treatment.

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EP1145

Pasireotide LAR Treatment for Non-functioning Pituitary Adenoma: A Case Report

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Introduction
Non functioning pituitary adenomas (NFPAs) are the most common type of pituitary tumors and are often invasive, resulting in high relapse rates. The post-surgical treatment for NFPAs remains a debated issue and include radiation therapy and additional surgery. Several clinical studies have demonstrated that dopaminergic and somatostatin receptors (SSTRs) are widely expressed in NFPAs. Furthermore, recent studies have shown the potential effectiveness of somatostatin analogues in the medical management of NFPAs. Although the data are limited and controversial, NFPAs express SSTR5 and SSTR3 at high levels. Pasireotide, a multireceptor-targeted somatostatin analogue with high affinity for SSTR5, may be beneficial in the management of NFPAs.
Case presentation
We report the case of a 33-year-old female with a history of surgical resection for a macro NFPA in 2010. Despite treatment with cabergoline (0.5 mg once a week), a residual tumor in close proximity to the right cavernous sinus continued to progress on follow-up post-surgery. In 2017, the patient underwent a second endoscopic resection. She did not experience any postoperative pituitary hormone deficits. However, subsequent radiological follow-up scans showed a progressive increase in the size of the residual tumor. In May 2018, the patient was evaluated by the multidisciplinary pituitary board, which suggested performing a PET-CT scan with Gallium that highlighted focal distribution of the receptor tracer on the right side of the sellae. Furthermore, histological revision of the slide showed negative expression of SSTR2A and positive expression of SSTR5. Subsequent radiological follow-up scans showed a progressive increase in the size of the residual adenoma. In December 2020, the patient's case was re-evaluated by the pituitary board, and radiation therapy was not recommended because of the young age and absence of hypopituitarism. Approval from the Ethics Committee was requested to use Pasireotide LAR as a therapeutic option for compassionate use. In May 2021, the patient started pasireotide LAR 40 mg intramuscular every 28 days. After 18 months of treatment, the residual adenoma showed no further progression on neuroimaging. The patient had good tolerance of the drug with no adverse events.
Conclusion
In this report, we describe a case of a NFPA negative for SSTR2A treated with pasireotide LAR. Our findings suggest that pasireotide LAR may be a treatment option for young patients affected by invasive non-functioning pituitary adenomas positive for SSTR5 who are not candidates for radiation therapy. Clinical studies could expand our single case observations.

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EP1146

Normal adult height in a pacient with untreated congenital hypopituitarism: a case report

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With congenital hypopituitarism, the clinical manifestations of pituitary hormone deficiencies usually appear during infancy or early childhood. Typically, one or more anterior pituitary hormones are deficient, and the most severe manifestations include neonatal hypoglycemia, electrolyte imbalances and failure to thrive. We present the case of a 43 year old male, with cardiovascular and metabolic comorbidities (arterial hypertension, type 2 diabetes mellitus), with no prior hospitalizations except for an episode of anaphylaxis, that was referred to the department of Endocrinology when a low FT4 was detected (0.5ng/dl) in the presence of a normal TSH. The patient was hemodynamically stable, and clinical examination revelead a height of 182.5 cm (+0.83 SD for age and sex according to national growth charts), weight = 81.5 kg, BMI = 24.5 kg/m2, pale, dehydrated skin, pectus excavatum, long, thin, laterally deviated fingers, an arched palate, as well as absent secondary sexual characteristics and congenital cryptorchidism. Endocrinological examination revelead corticotroph, tireotroph, gonadotroph and somatotroph insufficiency; undetectable estrogen and testosterone; and a prolactin level towards the lower limit of normal; and substitution treatment with Levothyroxine and Hydrocortisone was promptly initiated. Further evaluation revelead a normal ingestion and output of fluids (~1.5L/day), ruling out diabetes insipidus. Imaging studies included an abdomino-pelvic ultrasound, that releaved hypoechoic, homogenous masses in both the right and the left inguinal canal. Dual X-ray absorption bone densitometry revelead osteoporosis. Bone age was 17 years according to the wrist X-ray. MRI of the sella turcica showed a small remnant pituitary (~4.3mm height) with discreet intrasellar herniation of the suprasellar cisterna. Genetic investigations are currently underway (mlpa p018 SHOX, karyotype). While the hormonal profile and the presence of bilateral cryptorchidism suggests congenital CHPD, a surprising discrepancy was the patients' normal stature. Based on the existing literature, with around 10 similar cases described up to date, one possible explanation would be a coexisting genetic disorder associated with tall stature, such as [1] Marfan syndrome – rulled out by negative Ghent criteria score and further imaging studies (hand, foot and hip X-ray; echocardiogram; ophthalmological consult), [2] mutations in genes related to tall stature, such as SHOX duplication – genetic tests are ongoing or [3] the total absence of estradiol leaving the growth plates open, allowing growth through mechanisms independent of GH/IGF1, such as hyperinsulinism.

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EP1147

Presentation of A Patient with an EPI Attack and Apoplexy of A Pituitary Macroadenoma

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A 57-year-old female patient was presented to the neurologist in the ER because of her first grand mal-type seizure. Initial examination in the emergency department confirmed hyponatremia (Na 131 mmol/l) in laboratory findings, while CT scan of the brain and EEG were normal. During hospitalization, additional laboratory and imaging studies were performed. Neuroradiological examination was performed (CT scan of the brain, MRI of the brain and MRI of the pituitary gland), which confirmed the voluminous hippocampus on the left side and extremely widened sella turcica, with a septated cystic formation inside. The infundibulum was drawn to the right, the neurohypophysis was gracile, while the optic chiasm is drawn caudally. These were corresponded to the apoplexy of the pituitary gland (condition following haemorrhage in the area of the pituitary adenoma), which was accompanied by cystic degeneration. Hormonal tests were also performed and the results confirmed hypopituitarism (TSH was 0.90 mIU/l, fT3 4.4 pmol/l, fT4 5.9 pmol/l, FSH 1.0 U/l, LH < 0.1 U/l, estradiol 0 pmol/l, cortisol 157 nmol/l, prolactin 214 mU/l). An ophthalmological examination excluded visual field defects. Replacement therapy was initiated with levothyroxine at a dose of 75 mg and hydrocortisone 10 mg in the morning and 5 mg in the afternoon. During hospitalization her clinical condition improved and there was spontaneous recovery of serum sodium in the laboratory findings. An endocrinological control with new laboratory findings was recommended in 3 months and a control MRI of the pituitary gland in 6 months. The cause of the epilepsy was not found and further neurological monitoring is required.
Conclusion
Epi attack as s first presentation of pituitary macroadenoma.

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EP1148

Major improvement of diabetes insipidus 15 years after diagnosis of panhypopituitarism in a patient with pineal germinoma – a case report

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Pineal germinomas account for the majority of intracranial germ cell tumors. Surgery and radiation are usual management options, and secondary hypopituitarism can ensue after both. Diabetes insipidus is particularly common after surgical removal of pineal tumors, but improvement in polyuria and polydipsia years after surgery is exceedingly rare. Here, we present the case of a 49-year-old male, who was diagnosed with a pineal germinoma at the age of 20, which was surgically removed and then irradiated. The patient went without treatment until the age of 30, when he was hospitalized for inaugural diabetic ketoacidosis, and diagnosed with type I diabetes mellitus, as well as secondary panhypopituitarism. Insulin therapy, as well as hormone substitution treatment with levothyroxine, hydrocortisone, testosterone and desmopressin, was immediately started and the doses were adjusted several times during routine follow-up consultations. For the past several years, the patient has been on a steady dose of levothyroxine, prednisone and testosterone undecanoate; as well as desmopressin lyophilisate, with doses between 180 and 240 mg per day. However, recently, the desmopressin dose has been gradually lowered to 120 ug/day, and the patient was admitted for a routine check-up in our Clinic. Upon monitoring fluid ingestion and output, both were around 1 liter/day, so the desmopressin dose was gradually lowered to 30 ug/day, in the evening. One month later, fluid intake and output were roughly 2-2.5L/day under that dose. Because of that, Desmopressin treatment was stopped, and fluid intake and output increased to 4L/day. Upon reintroducing 30 mg Desmopressin daily, those values normalized. Another interesting finding was that the patient's testosterone levels repeatedly came back high-normal, despite being towards the end of the interval since the testosterone injection. This was interpreted in the context of the patient's psychiatric medication (Tianeptine, Haloperidol, Carbamazepine), which could alter SHBG levels. SHBG was measured, which came back within normal limits (80.1nmol/l). Serum βHCG levels were also normal (<0.1 mIU/ml), so further evaluation could involve measuring βHCG in CSF to assess for early recurrence. One surprising feature of this case was the sudden decrease in the Desmopressin necessary, after years of being on relatively high doses; so far, the literature has only described two similar cases, without identifying an underlying reason. This underlines the need for long to very long term follow-up in patients with secondary panhypopituitarism, and poses an interesting question for future research – what could be the reason for this suddenly quenched thirst?

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EP1149

Excessive production of chromogranine A in a meningioma with somatostatin receptors expression confirmed by GA68 -DOTATATE PET

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Background
Chromogranin A (CgA) is the most abundant granin in gastroenteropancreatic neuroendocrine tumors (GEP-NETs). As a tumor marker is moderately sensitive and nonspecific. Meningiomas are benign brain tumors that are usually to recur. Studies have shown *in vitro* and *in vivo* that meningiomas, regardless of histology and classification, express somatostatin receptors (SSTRs). GA68-DOTATATE PET is an exciting imaging modality that has shown significant advantages over conventional imaging in diagnosis and management of NETs.
Case report
This is a 56-year-old female patient who in 2021 presented an episode of high blood pressure accompanied by facial flushing and sweating. Secondary hypertension was screened with negative results including catecholamines and methanephrins, and elevated chromogranin A was detected. octresocan was requested, which showed a hyper-enhanced focus in the left paramedian frontal region that was confirmed by magnetic resonance imaging as a 9mm meningioma. An entero-MRI was also performed to rule out other more frequent NET locations, the study was negative, despite the fact that the patient was asymptomatic and maintain her blood pressure under control with a single drug, given persistently elevated CgA levels with a maximum peak of 18,846ng/ml, it was decided to complete a study with GA68 DOTATATE PET, which confirmed the unique existence of a hyper-uptake focus in the left paramedian frontal region compatible with meningioma without appreciating other foci that suggest the presence of tumor lesions with somatostatin expression, the patient was diagnosed with mengioma with somastatin receptor expression. Due to the size, finding the patient asymptomatic is decided jointly by the patient and the neurosurgeon to maintain observation without intervention for the moment.
Conclusions
PET imaging is being increasingly used to supplement MRI in the clinical management of brain tumors. A high expression of somatostatin receptor 2 (SSTR2) is found in all meningioma. [68Ga]Ga-DOTA-SSTR PET tracers are SST analogs with a high binding affinity to SSTR type 2, which make them an effective tool for imaging meningioma.

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EP1150

A case with pituitary metastasis from breast cancer presenting with hypernatremia

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The tumors that metastasis to the pituitary gland is a rare condition and generally are seen in patients in advance disease. The most common metastasis arises from breast and pulmonary cancer. We report a case of a 53 years old women with invasive ductal carcinoma diagnosed in 2017, previously treated with left radical mastectomy followed by — cycles of chemotherapy and radiation. In 2022 her disease recurred with bone metastasis. She started again the chemotherapy. One month after the last cycle of chemotherapy she presented at our emergency department with the following symptoms poor appetite, progressive general malaise, drowsiness, blurred vision, watery diarrhea, polydipsia, polyuria, nocturia. Initial laboratory work revealed hypernatremia with sodium of 157 mEq/l (136 - 148 mEq/l), low TSH 0.04 mIU/l (0.27-4.2 mIU/l), free T3 1.3 ng/ml (2.0 - 4.4 pg/ml), low free T4 0.83 ng/dl (0.93 - 1.7 ng/dl). Low LH 1.74 mIU/ml (7.7-58.5 mIU/ml) and FSH 6.92 mIU/ml (25.8-134.8 mIU/ml). ACTH 2.49 pg/mL (7.2-63.3 pg/ml), random cortisol 203 nmol/l (68.2-327 nmol/l) and a very high level of prolactin 2395 mIU/l (102-496 mIU/l), ADH 4.3 pg/ml (2-12pg/ml), GH 0.21 ng/ml (0.126-9.88). Hypernatremia and hypopituitarism prompted further studies: magnetic resonance of the pituitary region was performed. MRI with gadolinium revealed a pituitary mass 9.9 × 7.4-mm, isointense on T1 weighted images heterogeneously involving the infundibulum diameter 4.3 mm with multiple cerebral metastasis. These findings were highly suggestive of pituitary metastasis from her metastatic breast cancer. During the hospitalization she was treated with hormone therapy and was send to the oncology department for further treatment.
Conclusion
We describe a case of invasive ductal carcinoma with pituitary metastasis (PM). Aalthough rare, PM should remain in the differential of symptomatic pituitary dysfunction so proper diagnosis and treatment can be performed. Endocrine abnormalities should be corrected. Unfortunately, the presence of PM portends a poor prognosis

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EP1151

Non-functioning adenomas submitted to surgery: clinical characterization and outcomes

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Introduction
Nonfunctioning pituitary adenomas (NFPAs) are a heterogeneous group of tumors with different presentations. Clinical management of these tumors is complex. Our aim was to evaluate the clinical characteristics/postsurgical outcomes of NFPAs and to identify predictive factors of good response to surgery.
Methods
Retrospective analysis of NFPA, who underwent surgery and followed in our hospital, from 2015-2022.
Results
We evaluated 15 patients (60%-male), whose median age at NFPA diagnosis was 59 (45-86) years. Adenomas were incidentally identified in 2 patients. Visual

disturbances were the most common presenting symptom (67.7%). 47% of patients had ≧1 pituitary deficits and 1 patient had panhypopituitarism. Gonadotropic axis was the most commonly affected (60%). At diagnosis, hyperprolactinemia was present in 20% of cases. Preoperative ophthalmologic evaluation showed a visual field deficit in 64% and a significant decrease in visual acuity in 40% of the patients. Preoperative MRI studies displayed adenoma diameter of 29 ± 16.2mm. Cavernous sinus (CS) was invaded in 47% of the patients and proximity/compression to the optic nerve/chiasm was present in 14 patients. Fourteen of these tumors were categorized as gonadotroph adenomas and 1 as silent corticotroph adenoma (SCA). 33% of the patients showed Ki67 values >3%. Patients with preoperative hypopituitarism, 4/7 (57%) showed improvement of pituitary function (PF) at one year. Improvement of neuro-ophthalmological symptoms was observed in all patients after surgery. Complete removal of the tumor was observed in 5 (33%) patients. Residual tumor (RT) was documented in 7 (47%) patients after first intervention. Three patients required a second surgery due to tumor regrowth, a median of 81 (60-276) months after first intervention. A fourth pituitary operation was performed in 1 patient. Stereotactic radiosurgery with gamma knife was used in one patient due to tumor progression (single case of SCA). Hyperprolactinemia at diagnosis tended to be more frequent in the group that recovered PF ($P = 0.091$). RT after surgery tended to be more frequent in the group with larger tumors ($P = 0.043$), older age ($P = 0.056$) and CS invasion at diagnosis ($P = 0.067$).

Conclusions

Patients with preoperative neuro-ophthalmological disturbances seem to benefit from surgery. In patients with tumors in progression and hypopituitarism, normalization of PF may be achieved with surgery. Hyperprolactinaemia and younger age at diagnosis, as well as tumor dimensions seem to be associated with a favorable prognosis. Our results highlight the need for a longstanding approach by a multidisciplinary team.

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A Case of Chronic Hyponatremia in Clinical Practice

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Hyponatremia - a decrease in serum sodium to 135 mmol/l or less can lead to serious complications. In patients with various pathologies and serum sodium levels of 120–125 mmol/l mortality reaches 23%, in levels less than 115 mmol/l - 50%. Biochemical verification of hyponatremia is not difficult. It is difficult to establish the cause and treatment of chronic hyponatremia. Patient S., 64 years old, was hospitalized in a state of alcoholic intoxication with a diagnosis of an extensive scalp wound of the back. History of myocardial infarction in 2020; in 2022 traumatic brain injury with traumatic subarachnoid hemorrhage. In the biochemical analysis of blood - low values of sodium are 113 mmol/l, potassium - 3.4 mmol/l and chloride - 77 mmol/l. As an emergency preoperative preparation, infusion therapy was administered, including a concentrated solution of sodium chloride. To prevent the development of alcoholic delirium, the patient was prescribed carbamazepine 200 mg 3 times a day. Therapy was carried out with a 3% solution of sodium chloride 150 ml boluses. Despite ongoing therapy, the serum sodium level did not exceed 116 mmol/l. The levels of the hormones ACTH, cortisol and thyrotropic hormone were normal. Urinary osmolality was 200 mOsm/kg, sodium concentration was 81 mmol/l. Clinical diagnosis: severe hyponatremia, asymptomatic, due to the syndrome of inadequate secretion of antidiuretic hormone due to traumatic brain injury, alcohol intoxication, taking anticonvulsants, the presence of an extensive wound surface of the back. After unsuccessful correction of hyponatremia, a decision was made to introduce fludrocortisone into the treatment regimen, starting with a minimum dose (50 mg) and then increasing to 100 mg/day (to avoid loss of potassium levels) while maintaining the infusion of 10% potassium chloride solution at a dose of 50 ml. The serum sodium level stabilized at 120–124 mmol/l, and there was no sharp decrease in the level of potassium. By the end of the hospital stay, the sodium level increased to 126 mmol/l. The syndrome of hyponatremia has been classified as chronic hyponatremia. The patient was advised to lead a healthy lifestyle (exclude alcohol), add salt to food, limit drinking regimen. The presented clinical case demonstrates how difficult it is in clinical practice to verify the cause of hyponatremia and prescribe the optimal correction of chronic hyponatremia.

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EP1154

Prevalence, patterns, and characteristics of hypertension diagnosis and management in patients with Turner syndrome; Descriptive analysis of real-world data from the International-Turner Syndrome registry

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Introduction

Hypertension is common in patients with Turner Syndrome (TS), and they appear to have an increased predisposition with various proposed disease related factors; sex hormone imbalance, aortopathy, increased activation of the renin-angiotensin-aldosterone system, insulin resistance, growth hormone deficiency/resistance, adverse imprinting during fetal life and renal malformations. Despite high susceptibility and unique challenges in managing hypertension in this group, there exists no consensus on screening, classification, diagnosis, and management of hypertension, predominantly due to scarcity of evidence. Undiagnosed and/or poorly controlled blood pressure (BP) can be detrimental/-lethal in patients with aortopathy. In 2020, the International-TS(I-TS) registry was established within the International-Disorders of sexual differentiation (I-DSD) platform to fill gaps in the knowledge of TS and has a network reaching 260 centres in 63 countries.

Methods

All the centres registered under I-TS registry with patients ≥ 18 years were invited to participate in this retrospective multi-centre observational study. Pseudoanonymised data relevant to the study[karyotype, hormone-replacement(HRT), hypertension diagnosis, risk factors, management, morbidity] were either directly extracted from the registry or clinicians of relevent centres were requested to complete a formatted spreadsheet using routine clinic records.

Results

Complete data were available for 12/15 accepted-to-participate centres, from 11 countries, January 2022-2023. A total 181 patients [median-age 28.5 (range:18-71)years, median-age at TS diagnosis 11(range:0-34)years, and median BMI 25.2(range:18-44)Kgm^2] were included. Monosomy X(45,X) was the commonest (42%) karyotype and 64% of all patients were receiving HRT. Twenty-four(13.3%) patients had hypertension [Characteristics at diagnosis; median age 27(range:10-56) years, median systolic-BP 150(range:125-270)mmHg and median diastolic-BP 90(60-136)mmHg)]. The majority(18/24) had primary hypertension, and 4/6 with secondary hypertension had coarctation of the aorta.

The majority of those with hypertension (62%) were 45,X [$X^2(1,n=181)=4.779$, P0.029], and 91.6% were on HRT[median daily oetrogen dose:1(range:0-2) mg]. Many patients had coexisiting vascular risk factors; type 2 diabetes:16.7%, dyslipidaemia:33.3%, family-history:8.3%. The incidence of comorbidities potentially exacerbated by hypertension were; aortic disease:37.5%, congenital cardiac anomalies:12.5%, cardiac surgery:12.5%, renal anomalies:20.8%. The majority (21/24) received angiotensin-converting-enzyme inhibitors(ACEi)/ angiotensin-receptor blocker(ARB), and 6/24 were on beta-blockers(BB).
Conclusions
Hypertension is common in TS, with a high prevalence of associated risk factors and co-morbidities, highlighting the importance of development of specific guidance. In most cases, hypertension was diagnosed as primary hypertension, despite a young age of onset. ACEi/ARB and BB were the most commonly used medications. Furthermore, this study demonatrates, the potential advantage of inclusion of a large number of individuals, which is international in applicability, with capture of local site specific details.

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EP1155

Family building after diagnosis of premature ovarian insufficiency - a cross-sectional survey in 324 women

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Objective
The diagnosis of premature ovarian insufficiency (POI) is a traumatic event for many patients that involves poor fertility prognosis. After such diagnosis spontaneous pregnancies are rare. The alternatives for building a family are oocyte donation, embryo donation and adoption. However, we have few information on how many women with POI finally built a family after the diagnosis and which alternative they chose.
Design
We performed a cross-sectional, descriptive study.
Methods
We conducted a survey of all the women who consulted for POI in the department of endocrinology and reproductive medicine at la Pitié Salpêtrière between 31/05/1991 and 12/01/2021. We included patients who continued to be followed up regularly by our department or were contacted by mail or phone between June and September 2021. We excluded patients with Turner syndrome, POI secondary to oncological treatment and patients under 18 at the time of the survey.
Results
324 women with POI were analysed. Mean follow-up time between the first assessment in the service and the survey was 8,1 years. 41% of the women who wanted to build a family had children after the diagnosis: 53,9% by oocyte donation 1 woman by embryo donation, 5,6% after ovarian stimulation, 13,5% adopted and 25,8% had spontaneous pregnancy after a mean time of 2,5 years. Spontaneous pregnancy rate was 8,6% in the whole cohort.
Conclusions
Having children after a diagnosis of POI is not uncommon, but more often results from oocyte donation. This study will provide enlightened information for newly diagnosed women on the possibilities to build a family after POI diagnosis.

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EP1157

Prevalence of MTHFR polymorphisms and metabolic outcomes in Chilean women with Polycystic Ovary Syndrome

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Background
Polycystic ovary syndrome (PCOS) is a prevalent and multifactorial endocrine disorder, characterized by reproductive and metabolic alterations. However, the mechanisms that contribute to the development of metabolic abnormalities are not completely understood. Interestingly, women with PCOS show changes in folate and homocysteine levels suggesting an altered folate metabolism, which could be associated to changes in the methylation patterns of metabolic genes. Methylentethahydrofolate reductase (MTHFR) is one of the key enzymes in folate metabolism and it has been reported that polymorphisms in MTHFR gene could reduce the enzymatic activity.
Objective
The aim of this study is to assess the prevalence of SNP C677T (rs1801133) and A1298C (rs1801131) in *MTHFR* gene and their association with metabolic markers in PCOS women in comparison to control women.
Methodology
A total of 58 with PCOS without hormonal contraception and 77 control women with a BMI between 18 and 35 kg/m^2 (18-34 y.o.) were included in this study. Anthropometric measurements were carried out using standardized techniques and blood samples were obtained. To evaluate metabolic profiles, vitamin B12, serum and red blood cells folate (RBC) were measured, in addition to lipid and biochemical profiles, a food frequency questionnaire was performed. DNA analyses were performed in whole blood. Student's t-test or Mann Whitney test were applied for independent samples for compare both groups. To evaluate correlation, Pearson or Spearman was applied. For all analyses, a value of $P<0.05$ was considered significant.
Results
- PCOS women exhibited a significant increment in BMI in contrast to control group.
- PCOS women showed an increased Ferriman score, total testosterone, and free androgen index, accompanied by insulin-resistance.
- We found no differences in vitamin B12, serum folate and red blood cell folate, however, PCOS and control women do not achieve the daily dietary recommendations for choline and betaine.
- The distribution of C677T genotype frequency in our population was F(CC): 0.28, F(TC): 0.52 and F(TT): 0.2.
- The distribution of A1298C genotype frequency in our population was F(AA): 0.62, F(AC): 0.34 and F(CC): 0.03.
- The analysis of C677T and A128C shows that both polymorphisms are in Hardy-Weinberg equilibrium.

Conclusions
This is the first study that have reported the genotype frequency in Chilean women with PCOS. Further studies are necessary to determine the role of this genetic variants in this condition and circulating levels of choline and betaine should be measured, to validate this hypothesis due to their impact on metabolic dysfunctions.

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EP1158

BRCA1/2 Negative Bilateral Metastasized Breast Cancer Following Ovarian Stimulation: A Case Report

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Introduction
Breast cancer is the second most common neoplasm in women. Hormonal replacement therapy and combined hormonal contraception are established extrinsic hormonal risk factors for breast cancer. Therefore, the increase in the prevalence of infertility and the use of assisted conception techniques have raised questions regarding the potential risk of hormone-dependent neoplasms. We

report the case of a woman diagnosed with bilateral metastasized breast cancer soon after ovarian stimulation.
Case report
A 42-year-old woman with a 3-month history of worsening mechanical back pain visited the medical clinic with a dorso-lumbar CT scan report showing multiple vertebral lytic lesions (D3, D6, D10, L1, L2, L3, and L4) and two vertebral compression fractures (D6 and L5). She suffered from infertility and had just finished the third cycle of ovarian stimulation for oocyte collection. Before treatment, she underwent bilateral mammography and breast ultrasound, classified as BI-RADS 3, with no further follow-up. The patient had no family history of cancer. She was admitted for diagnostic assessment, which revealed stage IV bilateral breast cancer with multiple bone metastases (vertebrae, sternum, ribs, and the right femur). In the right breast, mass biopsy showed luminal A *like*/Her2 2+ FISH negative cT1 cN1 (metastases in the right axillary lymph nodes). In the left breast, mass biopsy showed luminal B *like*/Her2 2+ FISH positive cT1mf cN0. Vertebral biopsy of L5 revealed metastasis of the left breast cancer. Next-generation sequencing for the diagnosis of hereditary breast and ovarian cancer syndrome was unremarkable. She was referred to the oncology clinic and started on docetaxel, pertuzumab, trastuzumab, zoledronate, and radiotherapy. Follow-up showed stable disease nine months after the initiation of cancer treatment.
Conclusions
Current evidence indicates that ovarian stimulation does not appear to increase the risk of breast cancer. However, treatment with gonadotropins and estradiol is contraindicated in patients with this clinical entity. Thus, in this case report, ovarian stimulation may have enhanced the aggressive behavior of breast cancer, which was most likely present at the beginning of the infertility treatment. Hence, we raise the possibility of a distinct screening for breast cancer before, during, and after ovarian stimulation, whose consequences are still unpredictable regarding the risk and natural history of breast cancer.

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EP1159

Cytogenetic Study in 622 Infertile Men with Spermogram Abnormalities

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Background
Infertility affects 15% of couples. In 50% of cases, it can be explained by male infertility with abnormal spermatogenesis. Cytogenetic causes are identified in 15% of men with infertility.
Materials and Methods
We report the results of a cytogenetic study performed in infertile men with spermogram abnormalities collected at the Department of Congenital and Hereditary Diseases of Charles Nicolle Hospital in Tunis, over 12 years from January 2011 to February 2023. A standard karyotype on peripheral blood was performed in all patients.
Results
The number of infertile patients with spermogram abnormalities collected was 622. The blood karyotype showed the presence of a chromosomal abnormality in 81 patients (13%) of whom 69/81 had azoospermia, 9/81 had oligoasthenoteratospermia, 2/81 had cryptozoospermia and one patient had sperm degradation. The mean age at the first genetic consultation was 38 years. The chromosomal abnormalities identified were Klinefelter syndrome (47,XXY) in 56/81 patients (homogeneous in 50/56 patients and mosaic in 6/56 patients), a mosaic formula associating a 45,X population, and a second population with a normal or rearranged Y chromosome in 4/81 patients, an XYY formula in 3/81 patients and a Yq deletion in 3/81 patients, a supernumerary marker chromosome in 1/81 patients, a balanced structural rearrangement in 12/81 patients (4 Robertsonian translocations, 5 reciprocal translocations, and 3 inversions) and a 46,XX formula in 2/81 patients with male phenotype and gonadal dysgenesis.
Conclusion
Our study's high rate of chromosomal abnormalities identified in infertile men (13%) emphasizes the importance of performing karyotype in men with spermogram abnormalities to search for a chromosomal cause and guide management.

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EP1160

Overexpression of orphan nuclear receptor REV-ERB-alpha predicts recurrence in differentiated thyroid cancer

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Background
Altered circadian clock characteristics have been shown in malignant thyroid nodules. REV-ERB-alpha is a circadian clock component that functions as a transcriptional repressor which coordinates circadian rhythm and cell metabolism. However, the protein expression of REV-ERB-alpha has not been properly investigated.
Methods
Immunohistochemical analysis was performed on our in-house tissue microarrays. Immunoreactivity was evaluated using H-scores calculated by multiplying stain intensity by the percentage of positive stained cells. Recurrence-free survival was determined using a Kaplan-Meier curve.
Results
A total of 142 cases with differentiated thyroid cancer were evaluated. Nuclear staining of REV-ERB-alpha was upregulated in follicular epithelial cells of thyroid cancer but was absent in their normal counterparts. The H-scores were positively correlated with patients' age at diagnosis (Spearman's rank correlation rho = 0.310, $P = 0.0002$). Furthermore, increasing H-scores were associated with extrathyroidal extension (Jonckheere-Terpstra trend test, $P = 0.0005$), lymph node metastasis ($P = 0.036$), and tumor-node-metastasis stage ($P = 0.001$). Patients with higher REV-ERB-alpha expression in the tumor had a shorter recurrence-free survival (log-rank test, $P = 0.018$).
Conclusion
Thyroid cancer exhibits overexpression of REV-ERB-alpha. Nuclear expression levels have a prognostic significance in differentiated thyroid cancer.

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EP1161

Are there any benefits of probiotic or prebiotic supplementation in hypothyroid patients? A systematic review with meta-analysis

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Introduction
A number of studies indicate the presence of a thyroid-gut axis and the important influence of the gut microbiota on thyroid function. As prebiotics, probiotics and synbiotics show therapeutic potential in the treatment of intestinal dysbiosis, we aimed to evaluate the efficacy of their supplementation in patients with primary hypothyroidism.
Material and methods
We searched electronic databases (Ovid MEDLINE, Embase, CENTRAL), registers of clinical trials, and grey literature up to October 6, 2022. We included randomised controlled trials (RCTs). Our protocol was registered in PROSPERO (CRD42021235054).
Results
After screening 1721 references, we identified two RCTs including 136 hypothyroid participants in total. Meta-analysis after eight weeks of supplementation with predominantly Lactobacillus and Bifidobacterium strains indicated a clinically and statistically unimportant decrease in TSH (MD –0.19 mIU/l; 95% CI –0.43 to 0.06) and no effect on fT3 levels (MD 0.01 pg/ml; 95% CI –0.16 to 0.18). Data from single studies indicated no significant change in the levels of fT4, thyroid autoantibodies, BMI, levothyroxine doses, and severity of symptoms measured with validated scales. Only constipation scores showed significant improvement (MD – 8.71 points in Fecal Incontinence Questionnaire; 95% CI – 15.85 to –1.57; I2 = 0%).
Conclusion
Based on limited evidence from two randomised trials, there is no benefit from routine administration of probiotics or synbiotics in patients with primary hypothyroidism. We found no evidence on efficacy of supplementation with prebiotics.
Keywords
Prebiotics, Probiotics, Synbiotics, Thyroid, Hypothyroidism

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EP1162

Can we predict medical treatment failure in Graves' disease? 4-year follow-up data in a single centre

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Background
Graves' disease (GD) is the commonest cause of primary hyperthyroidism in iodine-sufficient areas. First-line treatment is a 12-18 month course of anti-thyroid drugs (ATD). However, around 50% of GD patients will relapse, requiring further assessment and definitive treatment with radioactive iodine or thyroidectomy. Identifying risk factors that predict relapse or treatment failure after stopping ATD is important in guiding management. Several risk factors have been reported in the literature from small with moderate-to-high risk for bias trials. We aimed to explore possible risk factors that can assist in identifying patients at high risk of relapse or medical treatment failure, to allow prioritisation for definitive treatment.
Methods
We retrospectively evaluated available data on consecutive patients with first presentation of GD who had positive TSH receptor antibodies (TRAbs), defined as TRAbs > 0.4 IU/l, at diagnosis at the Royal Berkshire Hospital and required ATD, between February 2017 and December 2018. Baseline demographics, TRAbs and thyroid function tests (TFTs) levels, and the presence of thyroid eye disease (TED) at diagnosis were recorded. TRAb titres were measured using the RSR Elisa TRAb 2nd generation assay. FT4 levels were measured using the Roche Cobas Elecsys Gen II assay.
Results
We included 154 individuals. The mean age was 51.6 years, 71.4% were female, and 15% had TED at diagnosis. The median (IQR) TRAb level was 2.7 (1.7, 5.7)IU/l, and the median (IQR) FT4 level was 52.6 (30.3, 81.4) pmol/l. The median follow-up of TFTs was 48 months. Median duration of ATD was 18 months. 102 (66.2%) participants relapsed or had treatment failure (i.e. ATD duration > 24 months). Gender did not affect treatment failure (females:65.5% vs males: 68.2%, *P*0.9). Median TRAb values were similar to those with no relapse (3.6 IU/l vs. 2.4 IU/l, respectively, *P*0.34). Subsequently, patients were divided into 3 sub-groups according to TRAb values (1st tertile: 0.5-1.9 IU/l, 2nd tertile: 2.0-4.3 IU/l, 3rd tertile: 4.4-31.0 IU/l). Individuals in the 3rd tertile, compared to the 1st, had a higher percentage of TED (30.4% vs. 11.1%, OR 3.5; *P*0.05), higher FT4 levels (72.4pmol/l vs. 31.6pmol/l; *P*0.0001) at the time of diagnosis, and significant risk of treatment failure (77.4% vs 54.2%, OR 2.9; *P*0.02).
Conclusions
Our study showed that patients who present with TED, higher TRAb and FT4 levels at the time of GD diagnosis are more likely to have medical treatment failure or relapse. Early referral for definitive treatment should be considered for such patients.

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EP1163

The Association of Immunotherapy-Related Thyroid Disorders and Mortality in Patients with RCC and Melanomas

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Background
Immune checkpoint inhibitors (ICPIs) are indicated as treatment for metastatic renal cell carcinoma (RCC) and melanoma, among other malignancies. This group of agents is associated with immune-related adverse events (irAEs). We aimed to further investigate the association of immune-related thyroid disorders (irTDs) with clinical outcomes and mortality rates in patients with RCC or melanoma who were treated with ICPIs.
Methods
We retrospectively analyzed all RCC and melanoma patients with normal baseline thyroid function who were treated with ICPIs at the Tel Aviv Sourasky medical center from 2016 to 2022. Demographic, clinical, and laboratory parameters were extracted using a big data platform (MDclone, Israel).
Results
We identified 149 ICPI-treated patients with RCC, of whom 108 (72.5%) were male. The average age at RCC diagnosis was 65.5 ± 10.6 years. Thyroid function abnormalities occurred in 42.3% ($n=63$) of ICPI-treated RCC patients. We analyzed 157 ICPI-treated patients with melanoma, of whom 92 (58.6%) were male. The average age at melanoma diagnosis was 68.5 ± 13.2 years. Thyroid function abnormalities occurred in 49% ($n=77$) of ICPI-treated melanoma patients. Thyroid disorders in both RCC and melanoma ICPI-treated patients were due mostly to hypothyroidism (clinical/subclinical) or thyroiditis, with hyperthyroidism occurring in fewer than 10% of patients. Mortality rates were significantly lower in RCC patients with evidence of irTDs compared with those who had no thyroid abnormality (38.1% and 62.8%, respectively. $P < 0.05$). This difference in mortality rates remained significant in subgroup analysis of men with and without irTDs (30.8% and 63.8%, respectively. $P < 0.05$) but not in women. No significant difference in mortality rates was found in melanoma patients with and without thyroid dysfunction, including in a gender subgroup analysis.
Conclusion
irTDs in patients treated with ICPI may impact prognosis in RCC. This effect was not observed in our cohort of patients with melanoma. More studies are needed to further investigate and characterize the underlying mechanisms and clinical relevance.

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EP1164

Coexistence of Behçet Disease and Graves

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Introduction
Behcet's disease (BD) is a systemic inflamatory disorder characterized by recurring oral and genital ulcers, uveitis, and skin lesions. Graves' thyrotoxicosis is caused by an autoimmune reaction to thyroid autoantigens. Thyroid receptor antibody testing is used to diagnose Graves' thyrotoxicosis. There has previously been no evidence of a link between thyroid autoimmunity and BD. We present a case of an adult male with BD coexistence, which is uncommon.
Case Report
A 49-year-old male patient presented with complaints of palpitations, marked sweating and weight loss (11 kg) for 4 months. The patient had deep vein thrombosis 8 years ago and was diagnosed with Behçet's syndrome while investigating the cause. He was receiving colchicine 2*1 treatment for Behçet's syndrome. On examination, the patient was sweaty and had hand tremors compatible with thyrotoxicosis. The patient had painless red eyes but no exophthalmos. Mild signs of thyroid eye disease were present. Blood tests revealed biochemical evidence of severe thyrotoxicosis and thyroid receptor antibody levels were elevated. Ultrasound scan of the thyroid and radioactive iodine uptake scan showed features consistent with Graves' thyrotoxicosis and a diagnosis of Graves' thyrotoxicosis was made. The patient was started on methimazole 30 mg and propranolol 20 mg twice daily. After treatment, the patient responded well with improvement of clinical symptoms and normalisation of thyroid functions. The patient is still being followed up in the internal medicine clinic for 4 years under colchicine, methimazole and propranolol treatment.
Discussion
BH can be considered an autoimmune disease due to its many features, including spontaneous remissions and relapses. There are reports that BD is associated with other autoimmune diseases. Since autoimmunity is responsible for the etiology of BH, the possibility of an increased incidence of autoimmune thyroiditis should be considered. Furthermore, there is a significant overlap in clinical features between different conditions such as oral ulcers, uveitis, and arthralgia, and this may occur in many of these conditions. However, the hypothesis regarding the role of antibodies in BD may also share a common ground in the pathogenesis of other autoimmune diseases. Although the limited data do not provide concrete evidence of any association between the two conditions, this case highlights the question of

whether their coexistence is due to a pathogenic relationship rather than mere coincidence.

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EP1165

'Colloid leak'-A lightening effect

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Background
Thyroidectomy is the common most common endocrine surgical procedure varies from Scalpel to Robotic transoral thyroidectomy. Colloid nodules are common and easily operable without any difficulty. We report a phenomenon where in the surgery becomes difficult and lead to complications if not thought with this phenomenon – colloid leak.
Material and Method
The endocrine surgeon (Associate Professor) has been involved in training of over 25 superspeciality endocrine trainers over a period of nine years in a tertiary referral high volume center. He has participated in 700 Thyroidectomies of which 250 thyroidectomies for colloid goiter. We have observed this phenomenon in 5 patients over 5 years in a tertiary referral centre in north India
Result
5 male patients (46.7 $\pm$ 12.1 years) had this colloid leak. Mean BMI was (22.4 $\pm$ 2.9). FNAC was colloid in all patients. 3 had colloid leak in all planes.2 had only per thyroidal leak. All patients had Recurrent Laryngeal nerve identified. In 1 patient only 1 parathyroid gland could be identified. Mean duration of surgery was 120 $\pm$ 12 minutes. Mean blood less was 10 ml $\pm$ 2.5ml. Mean duration of stay after surgery was 48. $\pm$ 12 hours. No permanent complication was observed. All patients operated within 2 weeks of FNAC. All HPT was colloid. Immunohistochemistry revealed IgG4 stained plasma cell aggregates in the line of colloid leak.
Discussion
This phenomenon was observed in muscular males in the colloid goiters where in there is leak of colloid after FNAC and this colloid elicited an inflammatory response in the surrounding tissues as evidenced by IgG4 positive immunohistochemistry staining for plasma cells. This phenomenon was more pronounced 5 to 7 days after FNAC. The planes were stuck and mobilization of gland was difficult in one patient a small cuff of muscle had to be removed. This fact of colloid leak causing chronic inflammation may be a harbinger of chronic changes and may a role in tumorogenesis
Conclusion
Astute Endocrine Surgeon should be aware of this colloid leak phenomenon and when found the dissection should be very careful to present complications during thyroidectomy.

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EP1166

Challenges in operating such monstrous goitres even in this era?

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A 45-year-old lady from the Iodine - deficient Himalayan belt presented to us with a gradually progressive, painless goiter for more than 20 years. Such goiters were common in her village. She neither had symptoms of hyper/hypothyroidism nor any compressive symptoms. She had four living issues and as per her, the goiter would increase in size during the second trimester of each pregnancy. On examination, she had a huge thyroid swelling involving both lobes and isthumus, measuring 20 $\times$20 cm with dilated veins over the swelling. The swelling was firm in consistency, moving with deglutition and had no retrosternal extension. There was no cervical lymphodenopathy. The diagnosis of an euthyroid multinodular goitre was made. Thyroid profile was normal; however, vocal cords could not be visualized during video laryngoscopy. CECT should retro tracheal extension. She underwent total thyroidectomy under General anesthesia. A 2-kilogram goiter was excised in toto, and the surgery lasted for 8 hours. Bilateral recurrent laryngeal nerve (RLN) and all four parathyroid glands were identified and preserved. However, intraoperatively she was found to have tracheomalacia hence, tracheostomy was done. She developed biochemical hypocalcemia on POD 2 and was started on oral calcium and vitamin D supplementation to which she responded well and became eucalcemic. Video laryngoscopy on POD 4 showed U/l paresis so tracheostomy care was continued. Video laryngoscopy on POD 12 showed bilateral vocal cords mobile, hence, she was weaned off tracheostomy gradually and was decannulated successfully on POD20. During the ICU stay patient developed ICU psychosis and required psychiatric care. Histopathology was reported as multinodular goitre. She now has normal voice, is eucalcemic and on thyroxine replacement. This case highlights the importance of thorough counselling of such patients with long standing goitre as these can cause tracheomalacia. Surgery in such cases requires utmost patience and always requires holistic hospital care by a multidisciplinary team. We almost lost the patient because of ICU psychosis when she became violent and tried to remove the tracheostomy tube by herself. Since these women are never exposed to hospital environment, she developed psychiatric rage and had to be treated accordingly.
Learning Points
1. Most of these goiters benign
2. Iodine Deficient belt
3. Huge MNG
4. Most women anemic
5. Intubation difficult-Awake preferred
6. Liberal incision
7. Strap muscles to be cut
8. RLN mostly on the surface
9. Tracheomalacia is common
10. Excess skin needs to be removed

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EP1167

Baseline Serum TSH Levels Predict The Thyroid Dysfunction In Cancer Patients Treated With Tyrosine Kinase Inhibitors And Immunotherapy

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Developments of the cancer immunology have increased the frequency of use of targeted therapies and immunomodulatory therapies. Although these treatments are effective on cancer cells, they also have toxicity on the thyroid gland. We aimed to evaluate the tyrosine kinase inhibitors(TKI) and immunotherapies-induced thyroid disorders, their relationship on disease prognosis and baseline serum thyroid stimulating hormone (TSH) levels effect on the development of thyroid dysfunction. This study was performed at a oncology center between January 2000 and December 2019. This study inclued 161 patients who were treated with immunotherapies and tyrosine kinase inhibitors. In this study, there were 161 patients whose basal thyroid function was normal. Thyroid dysfunction developed in 52 of 161(32.3%) patients. Hypothyroidism was developed in 44 of 52(84.6%) patients, and 28 of them were received L-thyroxin replacement treatment. Mean time to thyroid dysfunction development was found 14.7 weeks. By receiving operator characteristic (ROC) curve analysis, baseline serum TSH level was found as a potential predictive factor for development of hypothyroidism with a cut off value of 1.73 mIU/l, a sensitivity of 79.5% and a specifity of 56.9% and 87.3% negative predictive value(AUC:0,69, $P <$ 0,001). Progression-free survival (PFS) time was found to be longer in patients whom occurred thyroid dysfunction during sunitinib and pazopanib treatment. Our patient population receiving immunotherapies was small and so we could not

evaluated the relationship between thyroid dysfunction and PFS duration in these patient groups. More large-scale studies and longer follow-up is needed.
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EP1168

Papillary Thyroid Carcinoma Post Radioactive Iodine therapy for Graves' disease

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Background
Papillary Thyroid Carcinoma after Radioactive Iodine therapy for Graves' disease is rare with few cases reported in literature.
Presentation of case
A 28 years gentleman, presented with multiple non tender swellings in the anterior aspect of the neck, insidious in onset, initially started as a single swelling in the left side of the size 3×2 cm. Three years prior, he received I 131 therapy for Graves thyrotoxicosis. Thereafter, developed hypothyroidism after 6 to 7 months and was started on thyroxine supplementations at 50 μg/day. His mother was diagnosed with Papillary thyroid carcinoma age of 54 years. On head and neck examination, he had multiple swellings over bilateral neck with enlarged cervical lymph-nodes levels II, III,V.
Investigations
Ultrasound neck reported a right lobe vascular mid pole lesion of 7×7 mm with rim calcification, the isthmus contained a 8×6×5 mm well-defined lesion with micro calcification and increased vascularity, the left lobe mid pole had an ill-defined heterogeneous 28 x 21×16 mm lesion with micro calcification, the left neck had multiple in large lymph nodes. A guided FNAC was done from the thyroid nodules and cervical lymph nodes which was suspicious of Papillary thyroid carcinoma with cervical lymph node metastasis. Preoperative laryngoscopy bilateral vocal cords the mobile.
Treatment
He underwent Total thyroidectomy with bilateral central compartment lymph-node dissection, left selective lymph-node dissection(Level II &III) and right selective lymph-node dissection (Level II,III,IV&V). At operation, the left lobe was enlarged with a hard nodule measuring 2×2 cm, in the right lobe of the thyroid a small node measuring 0.5 cm was seen with extensive bilateral lymph node involvement in the central and lateral compartments. Visual identification and recurrent laryngeal nerve (RLN) neuromonitoring was done, left RLN and right RLN had electromyography signals of 1742μV and 572μV respectively. All four parathyroids were visually identified and preserved. Gross examination of the specimen revealed multifocal greyish white tumour tissue in both lobes of the thyroid. Histopathology reported multifocal papillary thyroid carcinoma of classical type. Seventeen out of the 26 resected lymph nodes in the central compartment and bilateral lateralcompartment showed metastatic foci. Based on the above findings a diagnosis of Classical multifocal papillary thyroid carcinoma pT1pN1bpMx was made. Postoperative period was uneventful and he made a good recovery.
Discussion
Literature rare in post radioactive ablation
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EP1169

Distant metastasis in a female patient with thyroid and breast carcinoma with low value of Thyroglobulin. Association between thyroid and breast cancer

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Breast cancer (BC) is the most common type of cancer and the leading cause of cancer-related death in women worldwide. A considerable number of these long-term survivors may therefore have an elevated risk of developing a second primary malignancy (SPM). Thyroid cancer (TC) is the most prevalent endocrine malignancy among women. Epidemiologic studies have indicated that patients with BC have a higher risk of developing TC as an SPM, and vice versa, than would be expected in the general population; and the risk of BC following TC is increased by 21% to 89% and that of TC following BC by 31% to 73%. We present a female patient with left breast carcinoma operated about 20 years ago with no medical documentation, recently diagnosed (January 2022) with papillary thyroid carcinoma TNM (AJCC 8th edition): pT2N0LV0Pn0 invasive in thyroid capsule and also in strap muscle with postoperative Thyroglobulin level of 26.7 ng/ml which indicated radioiodine ablation with 3570,29 MBq. At whole body scintigraphy were described multiple pulmonary secondary lesions, although thyroglobulin level decreased to 16 ng/ml. Structural imaging confirmed pulmonary, hepatic, splenic and even bone secondary lesions. Because the thyroglobulin level was discordant with multiple distant metastasis, we also investigate breast tumor marker CA15-3 = 442.74 U/ml (normal value: 0-32.4 U/ml) and structural images showed right breast carcinoma (bilateral breast carcinoma) confirmed by biopsy. Particularity of this case report is that secondary lesions appeared despite decreasing thyroglobulin level. Could we assume breast origin metastasis on radioactive WBS scintigraphy considering that breast cancer has sodium-iodine symporter expression? Or we could suspect thyroid related secondary lesions with abnormal low thyroglobulin level. The patient had progression of metastasis at 6 months after the radioactive iodine treatment, even if the thyroglobulin level was almost undetectable (0.3 ng/ml) suggesting an excellent biochemical response after iodine treatment for thyroid cancer.
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